OHIO STATE UNIVERSITY
AUG 30 1961
LIBRARY

HC

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY AUGUST 12 1961

RECEIVED
SEP 6 1961

TABLE OF CONTENTS

New Developments in Carcino-Chemotherapy F. BERGEL, F.R.S. 399
Some Aspects of the Pathology of Anaemia L. J. WITTS, M.D., SC.D., F.R.C.P. 404
Guanethidine in Treatment of Hypertension G. E. BAUER, M.R.C.P., F. J. T. CROLL, M.R.A.C.P., R. B. GOLDRICK, M.B., D. JEREMY, M.R.A.C.P., J. RAFTOS, M.R.A.C.P., H. M. WHYTE, M.R.C.P., and A. A. YOUNG, M.R.A.C.P. 410
Methoserpidine MARY C. HOLT, M.D., M.R.C.P. 415
Incidence of Hypokalaemia in Severe Hypertension OLIVER WRONG, B.M., M.R.C.P. 419
Intrathecal Tuberculin in Disseminated Sclerosis R. E. KELLY, M.D., F.R.C.P., and E. H. JELLINEK, D.M., M.R.C.P. 421
Faecal Excretion of Adenovirus in a Closed Community P. S. GARDNER, M.D., Dip.Bact., A. E. WRIGHT, M.D., D.P.H., Dip.Bact., and J. H. HALE, M.D., M.R.C.P. 424
Tabetic Gastric Crisis with Fluid Levels and Visible Peristalsis R. D. CATTERALL, M.R.C.P.Ed., A. J. C. LATCHMORE, M.S., F.R.C.S., and E. E. SHERWOOD-CUNDALL, M.B. 426

PRELIMINARY COMMUNICATIONS
Haptoglobin Types in Natives from the Kuru Region and other Parts of Melanesia. J. H. BENNETT, M.A., PH.D. 428
Cyproheptadine in Treatment of Urticaria. I. S. BAILEY, M.D., M.R.C.P. 430
Rapid Serological Diagnosis of an Outbreak of Influenza. N. R. GRIST, F.R.C.P.Ed., and others 431

MEDICAL MEMORANDA
Case of Primary Peritoneal Pregnancy. S. H. TOW, M.R.C.O.G. 432

BOOK REVIEWS 433

CLINICOPATHOLOGICAL CONFERENCE
Diseases of Different Systems 442

GENERAL ARTICLES AND NEWS
Regulation of Respiration: J. S. Haldane Centenary Symposium 449
To-day's Drugs 451
NEW APPLIANCES 450
OBITUARY 457
MEDICO-LEGAL 459
MEDICAL NOTES IN PARLIAMENT 460
UNIVERSITIES AND COLLEGES 461
VITAL STATISTICS 461
MEDICAL NEWS 463
QUESTIONS AND COMMENTS 465

LEADING ARTICLES
Aims of Criminology 436
Pathology of Pernicious Anaemia 437
Mass Radiography in Scotland 438

ANNOTATIONS
Tennis Elbow 439
External Cardiac Massage 440
Plant Hunters 440
Ammonium Chloride Acidosis 441
Drug Costs Again 441

CORRESPONDENCE
Abdominal Wound Dehiscence. JOHN BRUCE, F.R.C.S.Ed., and Sir WALTER MERCER, F.R.C.S.Ed.; G. A. BAGOT WALTERS, F.R.C.S.Ed. 452
Cooling of Operating Theatres. KENNETH H. PRIDIE, F.R.C.S. 452

SUPPLEMENT
Full Contents on First Page of Supplement
Cost of Pharmaceutical Services 121
Part-time Work for Government Departments 122
Correspondence:
Forgoing Salary Increases. G. W. M. MACKAY, M.D.; P. RANSOME-WALLIS, M.B. 122
A.R.M. Agenda. R. LL. MEYRICK, M.B. 122
Cost Plan in Hospital Building. T. W. FROGGATT, M.B. 123

CORRESPONDENCE—*contd.*
Spontaneous Biliary Peritonitis. H. T. FLEMING, F.R.C.S. 452
Schizophrenia in General Hospitals. M. S. BETHELL, D.P.M., and others 453
Premalignant Disorders of the Vulva. H. J. WALLACE, F.R.C.P., and I. W. WHIMSTER, M.B. 453
Fusion of Labia Minora. D. C. HUTFIELD, D.Obst.R.C.O.G.; W. RONALD D. FAIRBAIRN, M.D. 454
Patients with Trophoblast Tumours Wanted. JOHN YUDKIN, M.D., and others 454
Betamethasone. R. O. GILLHESPY, F.R.C.P.Ed. 454
Apnoea, Hypertension, and Conjunctival Oedema. G. H. BUSH, F.F.A. R.C.S. 455
Blood Transfusion for Mass Casualties. ROBERT J. HETHERINGTON, M.B. 455
Insertion of Intravenous Cannula. C. K. JONES, M.B. 456
Vagotomy for Peptic Ulcer. HAROLD BURGE, F.R.C.S. 456
Isoenzymes of Alkaline Phosphatase. DIANA M. CAMPBELL, B.SC., and D. W. MOSS, B.A., M.SC. 456
Medical V.C.s. E. E. BARNETT, F.R.C.S.Ed. 456
Over-attractive Capsules. DICK GLOVER, M.R.C.S. 457
Zip Fasteners on Trousers. O. G. WILDE, M.B. 457
Society for Cytologists. MOIRA MURRAY, D.P.H., and others 457

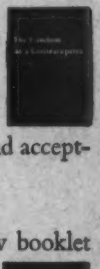
BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON W.C.1
No. 5249, WEEKLY, PRICE 3/-
Copyright © 1961
REGISTERED AS A NEWSPAPER

New literature on family planning

A recent survey has shown that over 70% of married women under 45 years of age are in favour of Family Planning, which explains why Doctors are receiving more and more requests for information.

These new booklets and leaflets give the latest information on conception control and will save Doctors' time when dealing with these enquiries.

The Condom protective as a Contraceptive. Written by the Director of Research at the National Committee on Maternal Health Inc., New York. This authority on the statistical evaluation of family planning analyses the effectiveness and acceptability of the protective in detail.



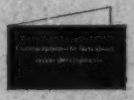
Modern Family Planning. A new booklet discussing the various methods of family planning written in simple language suitable for distribution to interested patients.

Diaphragm or Protective
A comparison of the two leading methods of conception control.

The case against Coitus Interruptus
An indictment of this method of conception control—its failure rate and its physical and mental effects.

The married woman's views on contraception. A survey based on facts revealed by a recent investigation of the opinions of married women about family planning.

Contraception—the facts about recent developments. An enquiry into the stage reached in the development of oral contraception — the advances to date, the interest of the general public, the known disadvantages and the long-term dangers.



Some criticism has, in the past, been levelled at Protectives on the grounds that they reduce sensitivity. A recent development by the London Rubber Company almost entirely overcomes such objections.

Copies of the leaflets listed above, will be sent on request, from

London Rubber Industries Ltd · Dept 294 · Hall Lane · Chingford · E.4

BRITISH MEDICAL JOURNAL

LONDON SATURDAY AUGUST 12 1961

NEW DEVELOPMENTS IN CARCINO-CHEMOTHERAPY*

BY

F. BERGEL, F.R.S.

Chester Beatty Research Institute, Institute of Cancer Research: Royal Cancer Hospital, London

The clinical treatment of all forms of cancer, including leukaemias and reticuloses, rests increasingly on combined operations of surgery, radiotherapy, and chemotherapy (Table I).

TABLE I.—*Treatment of Cancerous States*

Surgery	Radiotherapy	Chemotherapy
Pathologist Surgeon	Pathologist Radiotherapist Biophysicist	Pathologist Biochemist Experimental pathologist Chemist Clinician

While in the past surgery or radiotherapy or both were the sole methods to alleviate or cure malignant diseases, chemotherapy as the youngest member of the triad, after its victories in the battles against bacterial, spirochaetal, protozoal, and, so far, a few viral infections, is coming slowly into its own also in the field of neoplastic and related states. It is true, however, that there the systemic use of drugs has not the same degree of success as against foreign invaders (their effects, particularly *vis-à-vis* leukaemias, are more of a palliative than of a curative character), but their combination with either radiotherapy (additive or synergistic) or surgery (perfusional (Abel, 1960) or post-operative) or both is promising (Fig. 1). Such limited favourable results may give the experimentalist a little more time to find better remedies and to bridge the gap between the causation and behaviour of animal and human cancers.

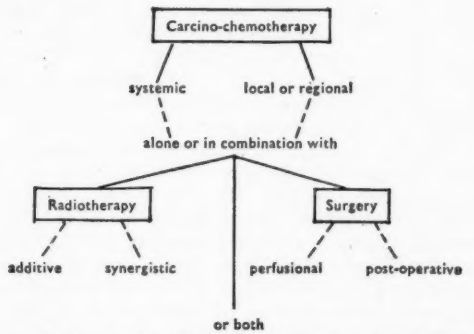


FIG. 1.—Relationship between chemotherapy, radiotherapy, and surgery.

*Read to the Third Plenary Session at the Annual Meeting of the British Medical Association, Auckland, New Zealand, 1961.

Groups of Agents

Below is given a brief review of the main groups of chemotherapeutic agents at present in use. This is followed by a presentation of some work in progress—by necessity of an experimental character—aiming at less toxic and more selectively acting remedies and at a possible increase in the susceptibility of the neoplasms to be attacked.

TABLE II.—*Anti-tumour and Anti-leukaemic Agents*

1. Biological Alkylating Agents — nitrogen mustards; methanesulphonates; ethylenimines, etc.
2. Antagonists and antimetabolites:
   Altered pyrimidines
   " purines
   " pteridines (folic acid)
   " vitamins (riboflavine, pyridoxine, nicotinamide, vitamin B_{12})
   " amino-acids and peptides
3. Products from micro-organisms and plants:
   Polysaccharides, antibiotics, podophyllotoxin, colchicin, etc.
4. Enzymes and co-enzymes:
   Xanthine oxidase, ribonuclease, pyridoxal phosphate-metal complexes
5. Hormones and antihormones
6. Immuno-bodies

In Table II the first group comprises the *biological alkylating agents*, so called because their main action consists in altering essential cellular constituents, such as nucleic acids, proteins, and enzymes, by alkylation and cross-linking, processes which lead to cell death. Among these agents are the *nitrogen mustards* (Fig. 2)

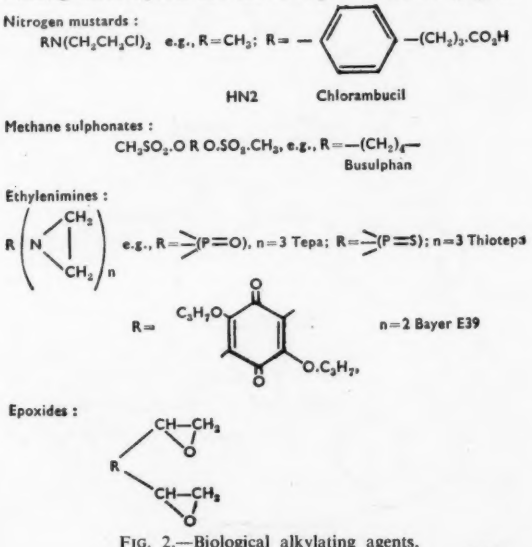


FIG. 2.—Biological alkylating agents.

with their warhead $N(CH_2CH_2Cl)_2$—examples, HN2, originally designed as war gas and now used during regional perfusion, its oxygen derivative nitromine, an aromatic acid, chlorambucil, which is clinically used in lymphocytic diseases; the *methane sulphonates*, such as busulphan ("myleran"), the standard drug for chronic myelogenous leukaemia; the *ethylenimines*, tepa, thiotepa, used clinically also in perfusions, and Bayer E39; and, finally, the *epoxides*, which are not very frequently applied.

The second group in Table II comprises the antimetabolites or metabolic antagonists, which as fraudulent substrates, products, cofactors, etc., are supposed to interfere with normal cell processes. Examples are (Fig. 3) 6-mercaptopurine and 5-fluorouracil, and 6-aza-uracil derivatives as antipurines and pyrimidines and aminopterin and methotrexate ("amethopterin") as antifolic-acid agents.

The third group represents products of microorganisms, such as antibiotics, actinomycin, mitomycin, or of higher plants. This is followed by the as yet purely experimental group of enzymes and coenzymes, to which we shall return later.

Finally, although belonging to the disciplines of endocrinology and immunology, there are the hormones, such as oestrogens—that is, stilboestrol (against cancer of the prostate) or androgens (against cancer of the breast)—and possibly antisera or vaccines.

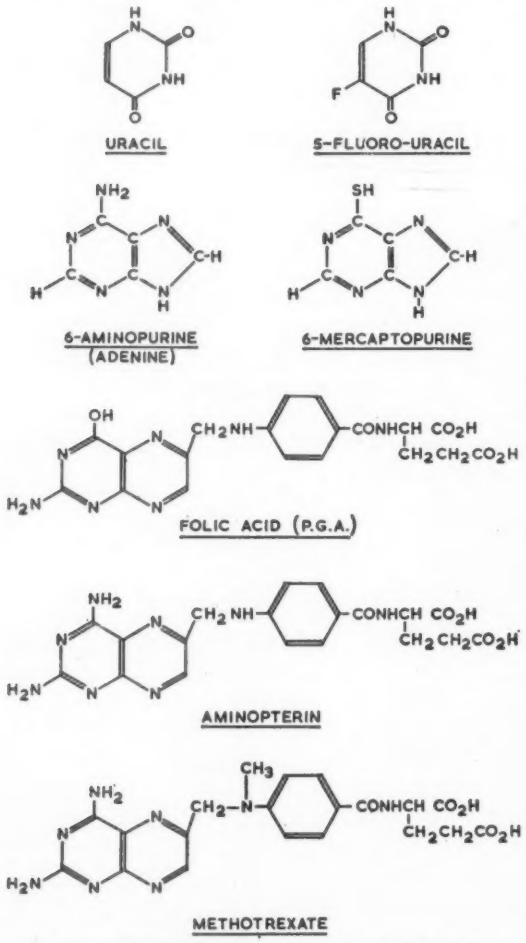


FIG. 3.—Antipyrimidines, antipurines, and antifolic acids.

Improvements of Cytotoxic Agents Sought and Achieved

After this "Cook's *tour de force*" an attempt should be made to answer the question: What is going on now in some laboratories all over the world to meet the challenge of the physician who demands improved drugs for systemic treatment and the more recent challenge of the surgeon who requires agents of reliability and safety for his regional perfusions? Time does not allow me to do justice to all contributions, but a selection of present-day investigations is offered.

Phenylalanine Derivatives

Starting with the postulates that the carrier moieties of biological alkylating agents are just as important as the "warheads" and that molecular structures related

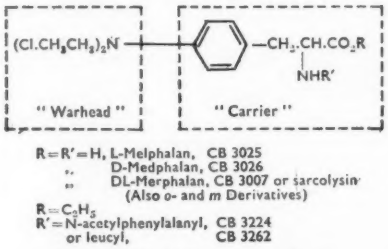


FIG. 4.—Phenylalanine derivatives.

to naturally occurring compounds might have advantages, some laboratories chose amino-acids, others sugar-like units, and, again, others pyrimidines as subjects of their studies which are being pursued in Britain, the United States, Japan, Hungary, and Russia. At the Chester Beatty Research Institute the chemists became interested, among others, in the phenylalanine (Bergel, 1958; Stock, 1958) series (Fig. 4). The *p*-mustard compound is now known as melphalan or PAM, in its racemic form as merphalan, or in Russia as sarcolysin (Larionov *et al.*, 1955). That melphalan is effective on human melanoma cells in form of tissue culture has been demonstrated by Ambrose *et al.* (1961), and is shown in Fig. 5 in comparison with chlorambucil.

Apart from placing the mustard warhead in different positions of the aromatic ring (*o*- and *m*-analogues studied in London by Connors *et al.*, 1960, and in California by Gram *et al.*, 1959; Osdene *et al.*, 1959), which, like the steric arrangements of the carrier moiety (L, D, DL) (Bergel and Stock, 1953), has a measurable effect on the anti-tumour activities (Walker carcinoma 256, S91 Cloutman mouse melanoma), the workers at the C.B.R.I. increased the size of the molecule by combining the original melphalan with a great variety of amino-acids (see Fig. 4). To mention only two examples, so-called N-acetylphenylalanyl-melphalan ester (CB 3224) and L-leucyl-melphalan ester (CB 3262) (Bergel and Stock, 1960) gave, so far only in animals, promising results, the former possessing an improved therapeutic index—that is, less toxic in proportion to its anti-Walker effect, the latter apparently gaining carcinostatic activities against a greater range of experimental tumours (S180 in the mouse, and sarcoma induced with benzpyrene in the rat) which had so far proved more resistant to other related compounds.

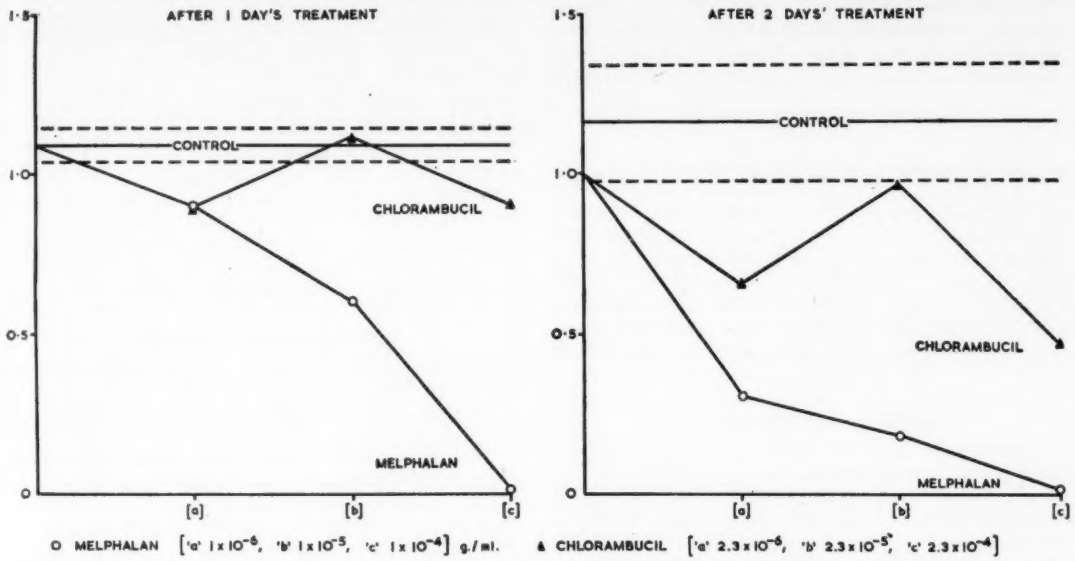


FIG. 5.—Effect of melphalan and chlorambucil on human melanoma cultures. After one day's and after two days' treatment. (By courtesy of Dr. E. J. Ambrose.)

Dimethanesulphonic Acid Esters of Sugar Alcohols

Another investigation under the direction of Timmis (Haddow *et al.*, 1958), who is the discoverer of the well-known antileukaemic drug myleran, led to the preparation of the methane sulphonic-diester of the sugar alcohol mannitol (Fig. 6). While its clinical testing is proceeding in America, the experimental data disclose a wide spectrum of activity with low toxicity and haemotoxicity.

"Latent" Drugs

This brings the review to another recent approach. So that the selectivity of agents for tumour tissues as against normal dividing tissue (bone-marrow, intestinal mucosa) would increase, a number of workers have taken an interest in so-called "latent" drugs—that is to say, drugs which are inactive but could become activated under certain *in vivo* conditions. While Danielli and his school (Danielli, 1961) have pursued this matter on a speculative basis, Ross and Warwick (1956) were the first to produce a deactivated azo-derivative of an aromatic mustard, CB 1414 (Fig. 7), which has aroused some interest in Canada and the U.S.A.

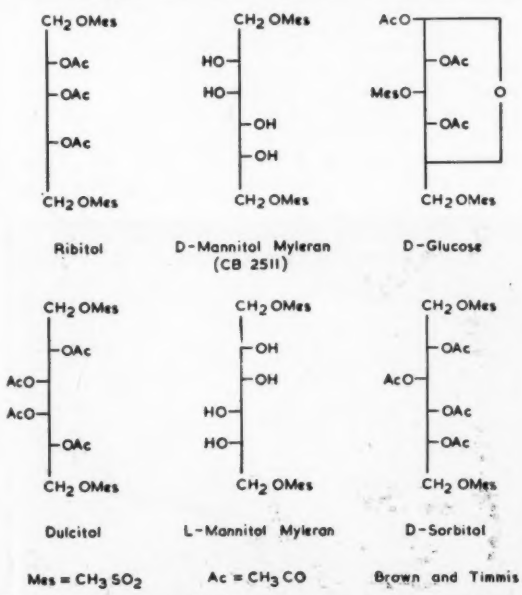


FIG. 6.—Dimethanesulphonic acid esters of sugar alcohols. (From Timmis and Brown, 1960.)

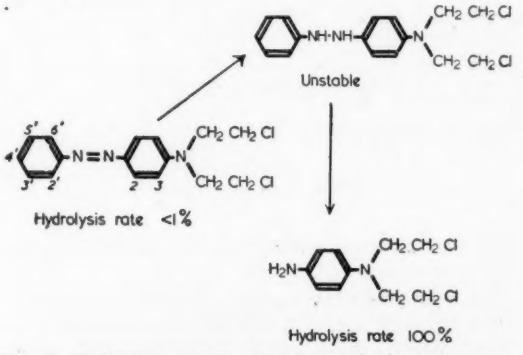
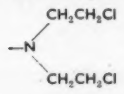


FIG. 7.—Reductive activation of chloroethylamino-azobenzenes. (By courtesy of Dr. W. C. J. Ross.)

Another grouping which keeps the warhead



in check, unless it is removed, is next to it either P=O as in phosphoric acid, or C=O in amides. A representative of the former is the drug cyclophosphamide ("endoxan," "cytoxan") (Fig. 8), synthesized by the Asta

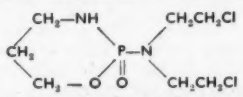


FIG. 8.—Formula of cyclophosphamide.

Werke in Germany (Arnold *et al.*, 1958), the idea based on the original work of Friedman and Seligman (1954) in the U.S.A., and of the latter a carbamyl serine derivative (mercasin) (Fig. 9), prepared by Wade (Bergel

FIG. 9.—Formula of carbamyl serine mustard, mercasin.

and Wade, 1959). Both drugs depend on a breakdown in the body, maybe induced by enzymic action (phosphoramidase and a "carbamase" respectively) to the active di-2-chloroethylamine (nor-HN2). While cyclophosphamide (Cancer Chemotherapy Reports, 1960) is in clinical use, mercasin, which additionally might be able to interfere with amino-acid metabolism, still awaits testing in man.

Antibiotics and Plant Products

Recent advances in the field of antibiotics and higher-plant products as anti-tumour drugs include the findings of Maddock *et al.* (1960) that Waksman's actinomycin D, a complex peptide, potentiated *x*-ray irradiation in mice and men, and that when applied simultaneously in cases of cancer in children (Farber *et al.*, 1960) (Wilms's tumour, etc.) led in a number of them to clinical cures. Otherwise there exists a constant stream of mould brews emanating mainly from industrial laboratories which are the subject of systematic large-scale tests by the American C.C.N.S.C., and from which from time to time an antibiotic with anti-tumour or antileukaemic effects is isolated. An older example is the discovery of azaserine and DON (Fig. 10) (Reilly,

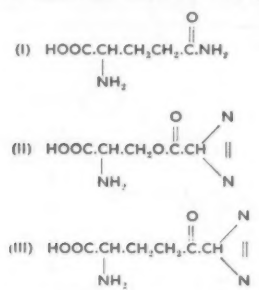


FIG. 10.—Formulae of glutamine (I), azaserine (II), and DON (III).

1958). The Japanese are also very active in this hit-and-miss venture, having isolated, among others, mitomycin (Cancer Chemotherapy Reports, 1959), which, while highly toxic, has a wide tumour spectrum.

Among higher-plant products colchicine from the autumn crocus, and, more recently, vincaleukoblastine (Noble *et al.*, 1958a, 1958b) from periwinkle have found entry into clinical medicine.

Metabolic Antagonists

It has been mentioned before that metabolic antagonists form a large part of the as yet slender armamentarium of the physician battling against leukaemias and neoplastic diseases. Work with respect to this group is proceeding at a considerable pace, perhaps not paralleled by a similar rate of practical achievements. There are so many building units and enzymic events in the cell with which one could interfere, the problem always being that such interference should preferentially involve the tumour cell. The difficult synthesis of 2′-deoxy-5-fluorouridine has put at the clinician's disposal a less toxic substance than the simple pyrimidine itself. 6-MP, still one of the mainstays in the treatment of acute leukaemias, has been transformed by the chemists into derivatives with less pronounced side-effects. Almost weekly new representatives of purine, pyrimidine, pyridine, and folic acid analogues or their enzyme inhibitors are produced, but so far only small advances are being recorded concerning their capability of hitting the abnormal cell harder than its normal counterpart. And the acute forms of leukaemia, although held in check for short periods, still have to find their match.

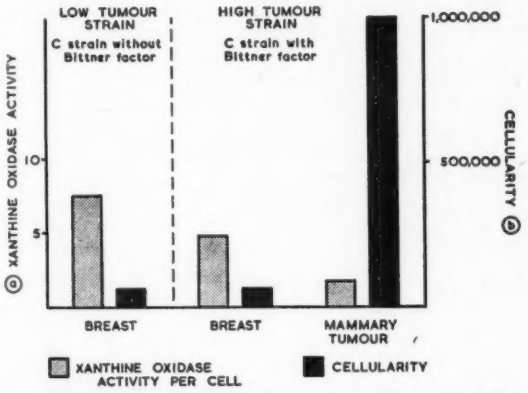
Speculative Developments

A point has been reached where the further question has to be asked: Will a continuation of the extensive work as sketched out above in a very brief manner lead to drugs or remedies with significantly greater efficacy? Or will the answer, if there is soon an answer, come from a different direction, emanating from a more physiological or biochemical approach? There is no time here to discuss the possible developments in the field of hormones, of immunological reactions, and of virology. Suffice it to say that the hormones, whether connected with sex organs or belonging to the corticosteroids, had, and have, some successes. The studies of antigen-antibody-complement properties of tumours are in their infancy (Zilber, 1961). Workers are battling with many difficulties, not the least those related to the distinction between the antigens of normal tissue, and additional, or missing ones, of neoplasms. And what about the viruses either as a causation or as a treatment of a few malignant states? From a purely clinical point of view they are at present just as elusive (Moore, 1961).

There remains one more speculation. If the development and establishment of malignancy were at least in part due to the loss of certain essential cellular constituents or to a faulty biosynthesis of one or another of them, would it be possible to initiate a replacement or substitution therapy which might achieve a degree of success at least similar to that with vitamins and amino-acids or hormones in cases of nutritional or endocrine deficiency diseases? A rational approach could only start with a detailed knowledge of all the biochemical properties and behaviour of the aberrant cell. Unfortunately we are still a long way from such a goal. More and more cases have been reported where

FIG. 11.—Spontaneous mammary carcinoma in C+ mouse.

quantitative differences in cellular constituents between cancer cells and comparable normal ones have been established, but no certainty exists whether these differences are of a primary or a secondary nature and whether they form a steady characteristic of histologically similar tumours. However, let us consider one example studied experimentally.



1. The enzyme activity per mammary cell increases during normal growth of breast.
2. The enzyme activity per mammary cell is lower in the cancer-susceptible than in the cancer-resistant mouse.
3. The enzyme activity per tumour cell is very low in comparison to the breast cell. Whether this fall in enzyme content per cell is associated with a fall in enzyme concentration within the cell is under study.

(a) μ moles $[+10^{-6}]$ xanthine oxidized/1×10^{-6} nuclei/min.
(b) Nuclei/mg. wet tissue.

FIG. 12.—Xanthine oxidase during carcinogenesis in mouse breast. (From Bergel *et al.*, 1957, p. 256.)

A number of years ago Haddow (Bergel *et al.*, 1957) put forward the working hypothesis that the enzyme xanthine oxidase, because it controlled the purine pool from which nucleic acids would derive and consequently regulate cell growth and division, might arrest cancer growth when injected into tumour-bearing animals. One of the few spontaneous tumours in the rodent, available to the experimentalist, is the mammary carcinoma in the so-called C3H and C+ mouse (Fig. 11). Lewin *et al.* (1957), while working at the C.B.R.I., established that there was indeed a deficiency of the enzyme in the tumour as compared with precancerous and completely normal breast (Fig. 12).

When de Lamirande (Haddow *et al.*, 1958) repeated Haddow's preliminary trials by injecting highly purified xanthine oxidase from cow's milk as prepared by Bergel and others (Haddow *et al.*, 1958), an arrest in the growth rate of the tumours occurred (Fig. 13).

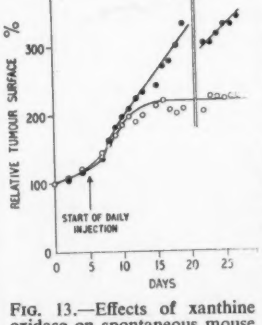


FIG. 13.—Effects of xanthine oxidase on spontaneous mouse mammary carcinoma. O—O, 18 treated mice. ●—●, 18 control mice given saline.

Is it possible to find a comparable biochemical for injection into the human patient suffering from one or the other form of cancer; would it be possible to overcome immunological complications if the material had antigenic properties; would it be active against a tumour in man in the way in which insulin of bovine origin, while not curing diabetes, controls the pathological effects of the disease? We do not know yet.

Summary

A considerable number of drugs for systemic and perfusion chemotherapy are at the disposal of the clinician. They are at present not ideal remedies, and thus have to remain in the hand of the specialist. However, improvements in toxicity and selectivity may follow the lines presented above. The practical use of immunotherapy and replacement therapy in clinical medicine depends very much on future progress, and, so it is believed, to a large extent on a concerted effort in many laboratories to create a series of tests which would assist in a biochemical characterization of human cancers. This, together with the old-established morphological description as given by the pathologist, should enable the clinician in collaboration with the practitioner to arrive at the right choice of treatment—surgery, radiotherapy, or chemotherapy, or any of their combinations—to remove the deadly sting from these up to now far too often killing diseases.

REFERENCES

Abel, L. A. (1960). *Brit. med. J.*, **1**, 952.
Ambrose, E. J., *et al.* (1961). Private communication.
Arnold, H., Bourseaux, F., and Brock, N. (1958). *Nature (Lond.)*, **181**, 931.
Bergel, F. (1958). *Ann. N.Y. Acad. Sci.*, **68**, 1238.
—— Bray, R. C., Haddow, A., and Lewin, I. (1957). In *Ciba Foundation Symposium on the Chemistry and Biology of Purines*, p. 256. Churchill, London.
—— and Stock, J. A. (1953). *A.R. Brit. Emp. Cancer Camp.*, **31**, p. 6.
—— —— (1960). *J. chem. Soc.*, p. 3658.
—— and Wade, R. (1959). *J. chem. Soc.*, p. 941.
Cancer Chemotherapy Reports (1959). Cancer Chemotherapy National Service Center, U.S. Public Health Service, No. 2, p. 3.
—— (1960). Cancer Chemotherapy National Service Center, U.S. Public Health Service, No. 8, p. 116.
Connors, T. A., Ross, W. C. J., and Wilson, J. G. (1960). *J. chem. Soc.*, p. 2994.
Danielli, J. F. (1961). In *Biological Approaches to Cancer Chemotherapy*, edited by R. J. C. Harris, p. 1. Academic Press, London and New York.
Farber, S., D'Angio, G. J., Evans, Audrey, and Mitus, Anna (1960). *Ann. N.Y. Acad Sci.*, **89**, 421.
Friedman, O. M., and Seligman, A. M. (1954). *J. Amer. chem. Soc.*, **76**, 655.
Gram, H. F., Mosher, C. W., and Baker, B. R. (1959). Ibid., **81**, 3103.
Haddow, A., de Lamirande, G., Bergel, F., Bray, R. C., and Gilbert, D. A. (1958). *Nature (Lond.)*, **182**, 1144.
—— Timmis, G. M., and Brown, S. S. (1958). Ibid., **182**, 1164.
Larionov, L. F., Khokhlov, A. S., Shkodinskaja, E. N., Vasina, O. S., Troosheikina, V. I., and Novikova, M. A. (1955). *Lancet*, **2**, 169.
Lewin, I., Lewin, R., and Bray, R. C. (1957). *Nature (Lond.)*, **180**, 763.
Maddock, Charlotte L., D'Angio, G. J., Farber, S., and Handler, A. H. (1960). *Ann. N.Y. Acad. Sci.*, **89**, 386.
Moore, Alice E. (1961). In *Biological Approaches to Cancer Chemotherapy*, edited by R. J. C. Harris, p. 365. Academic Press, London and New York.
Noble, R. L., Beer, C. T., and Cutts, J. H. (1958a). *Ann. N.Y. Acad. Sci.*, **76**, 882.
—— —— —— (1958b). *Biochem. Pharmacol.*, **1**, 347.
Osdene, T. S., Ward, D. N., Chapman, W. H., and Rakoff, H. (1959). *J. Amer. chem. Soc.*, **81**, 3100.
Reilly, H. C. (1958). In *Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity*, p. 62. Churchill, London.
Ross, W. C. J., and Warwick, G. P. (1956). *J. chem. Soc.*, p. 1364.
Stock, J. A. (1958). In *Ciba Foundation Symposium on Amino Acids and Peptides with Antimetabolic Activity*, p. 89. Churchill, London.
Timmis, G. M., and Brown, S. S. (1960). *Biochem. Pharmacol.*, **3**, 247.
Zilber, L. A. (1961). In *Biological Approaches to Cancer Chemotherapy*, edited by R. J. C. Harris, p. 231. Academic Press, London and New York.

SOME ASPECTS OF THE PATHOLOGY OF ANAEMIA

II. INVESTIGATION OF CASTLE'S HYPOTHESIS*

BY

L. J. WITTS, C.B.E., M.A., M.D., Sc.D., F.R.C.P.

Nuffield Professor of Clinical Medicine, the Radcliffe Infirmary, Oxford

By 1932 Castle's hypothesis that pernicious anaemia was due to the absence of an intrinsic factor in the gastric juice which reacted with an extrinsic factor in the diet to produce the haemopoietic factor had been generally accepted. There were still, however, certain reservations. There was doubt whether complete loss of the stomach in man inevitably led to pernicious anaemia, for it did not do so in animals, and at that time there were few patients whose life had been prolonged more than a year or so after total gastrectomy. As the number of survivors has grown we have learned that pernicious anaemia always develops if the patient lives long enough, though it may take several years for the body to exhaust its stores of vitamin B_{12} (Paulson and Harvey, 1954).

Another difficulty was that achlorhydria was thought to be quite common, 20 to 30% in the later age-groups after a single body-dose of histamine (Polland, 1933). Estimation of intrinsic factor by the Castle test was a long and arduous procedure, not without danger to the patients used as test subjects, so that no large series of individuals with achlorhydria but without pernicious anaemia was studied. Since the introduction of the augmented histamine test and similar methods of giving a maximal stimulus to the parietal cells we know that true achlorhydria occurs much less often than used to be believed and is always evidence of disease of the stomach (Witts, 1959). Of the patients with complete achlorhydria a moiety will also have lost their ability to secrete intrinsic factor (Callender, Retief, and Witts, 1960). The total number of such cases seems relatively large in relation to the prevalence of overt pernicious anaemia (Witts, 1960). Nevertheless, it is doubtful whether we need invoke any other factor than the exhaustion of the tissue reserves of vitamin B_{12} to explain the transition from larval to overt pernicious anaemia.

Stalemate and Break-through

It would not be true to say that research based on Castle's hypothesis languished during the fifteen or twenty years after his first publications. Indeed, a good deal of exciting work was done to which I shall refer. Nevertheless, so long as neither extrinsic factor nor intrinsic factor had been characterized chemically the pace was slow. The doubts which I have mentioned—whether Castle's hypothesis provided a complete explanation of pernicious anaemia, and the failure to produce pernicious anaemia in animals by gastrectomy—led to the supposition that achlorhydria and loss of intrinsic factor might merely set the stage for pernicious anaemia but that some other factor was necessary for its complete development, an idea which, as I have just hinted, has not yet been completely abandoned.

Thus interest was revived in the long-mooted possibility of an intestinal factor in pernicious anaemia, and a series of clinical and experimental observations led to the recognition of a group of anaemias associated with stenosis, anastomosis, and massive diverticulosis of the small intestine which we now know to be due to impairment of absorption of vitamin B_{12} (Faber, 1895; Cameron, Watson, and Witts, 1949; Badenoch, 1960). Much of the experimental work was done on the rat, and when Watson and Florey (1955) subsequently demonstrated the value of the gastrectomized rat in the study of the absorption of vitamin B_{12} we found that we had come back full circle to pernicious anaemia itself, and what Castle (1959) has called the years of the rat had begun in research on pernicious anaemia.

The isolation of folic acid in 1943 simplified our problems by indicating that there was a range of megaloblastic anaemias, usually of nutritional or intestinal origin, which were due to lack of folic acid and not of the liver principle active in pernicious anaemia, but by and large folic acid has not proved an easy tool to use in the investigation of the anaemias (Girdwood, 1960). The nature of the folic acid activity normally present in human serum and plasma, and its assay, are still under investigation (Herbert, 1961). We cannot estimate the tissue levels of folic acid in the same simple way that we can estimate the level of ascorbic acid in the white-cell layer of the blood. Tests dependent on the excretion of doses of folic acid in the urine or the clearance of folic acid from the plasma are indirect and difficult to interpret. Quite early on we came to the conclusion in Oxford that the way to the assessment of the folic acid status of the organism did not lie in this direction, and though some elegant work has since been done by others it has not changed our opinion (Spray, Fourman, and Witts, 1951; Spray and Witts, 1953). This is not to deny that Girdwood's (1953) test, which depends on comparing the amounts of folic acid excreted after subcutaneous injection and oral ingestion, has proved useful in the investigation of steatorrhoea.

The situation has not been radically altered by the introduction of tritiated folic acid—that is, folic acid in which some of the hydrogen atoms have been replaced by the radioactive isotope tritium (Johns, Sperti, and Burgen, 1961). The most useful method at present is one which depends on the role of folic acid in metabolism. There is evidence that formiminoglutamic acid (F.I.G.L.U.), an intermediate in the metabolic breakdown of histidine, accumulates in the urine of men and animals which are deficient in folic acid (Broquist, 1956; Silverman, Gardiner, and Condit, 1958). At first F.I.G.L.U. could be estimated only by complicated microbiological methods, and results, though encouraging, were slow in coming forward (Spray and Witts, 1959). However, the introduction of a relatively simple electrophoretic method of estimation (Knowles, Prankerd, and Westall, 1960) has changed all this, as radically as the electrification of a railway line changes a quiet suburb; we can look forward to a spate of papers on F.I.G.L.U.

The big surge forward in the study of the megaloblastic anaemias came with the isolation of vitamin B_{12} in 1948, the associated discovery of microbiological methods of estimating the level of vitamin B_{12} in the serum, and the subsequent labelling of the vitamin B_{12} molecule by the incorporation of radioactive cobalt so that it could be used in tracer studies of the absorption and metabolism of vitamin B_{12}. At one blow two unknowns had been eliminated in the equation f+g=h, which was based on the assumption that a food factor

*The second of two Lumleian Lectures delivered before the Royal College of Physicians of London on April 11 and 13, 1961. The first lecture appeared in last week's issue

(f) reacted with a gastric factor (g) to give rise to a haemopoietic factor (h), and the stage was set for the characterization of the intrinsic factor (g). The way was finally open to a rational classification of the megaloblastic anaemias (Witts, 1956). They can be divided vertically, according as they are due to deficiency of vitamin B_{12}, folic acid, or both; or they can be divided horizontally, at the level of the cause of the deficiency —diet, stomach (in avitaminosis B_{12} only), intestine, or the organism itself in the relative deficiencies of folic acid which may sometimes be observed in pregnancy, idiosyncrasy to barbiturates, and pathologically accelerated blood formation (Chanarin, Dacie, and Mollin, 1959).

Intrinsic Factor

When I surveyed the material which I had collected for these lectures, I found that there were far more references to papers on intrinsic factor than on any other topic. This was not because there had been a greater accumulation of knowledge about intrinsic factor than, say, the antianaemic factor, but rather the reverse. Indeed, it is a common experience, as inspection of the bulky literature on blood coagulation will confirm, that when biologists and clinical scientists carry out researches with substances whose purity and chemical characteristics are not known, much of their work is likely to be inconclusive. Had research been centrally planned, it is certain that a much greater effort would have been put into the isolation of intrinsic factor. Fortunately there have been a number of reviews of this copious literature, of which Gräsbeck's (1960) is one of the most recent and comprehensive.

The isolation of vitamin B_{12}, or cyanocobalamin, led to the hypothesis that intrinsic factor acts as a carrier in the absorption of vitamin B_{12}. When pure vitamin B_{12} became available in quantity it was discovered that there are two mechanisms of absorption. If vitamin B_{12} is administered in milligram quantities a small percentage of the dose, usually quite enough to maintain health, is absorbed without intrinsic factor. This is presumably achieved by mass action, though the details of the process are not known. At any rate this mechanism is effective in pernicious anaemia and total gastrectomy. Absorption can occur by the same mass action through the oral, nasal, respiratory, and rectal mucosae. If vitamin B_{12} is administered in microgram quantities, such as are present in the diet, intrinsic factor is necessary for its absorption, and little or none is absorbed in pernicious anaemia or after total gastrectomy.

When physiological doses (0.5 to 2 μg.) of radioactive vitamin B_{12} of high specific activity are given to normal people or are given along with intrinsic factor to patients with pernicious anaemia, little or no radioactivity can be detected in the plasma within the first four hours of the test and the peak concentration occurs at eight to twelve hours. If an oral dose of 50 to 300 μg. of radioactive vitamin B_{12} is given in pernicious anaemia there is an entirely different curve, with an early rise in radioactivity in the plasma and a peak concentration usually at three to six hours. The watershed between the physiological and the pharmacological channels of absorption is probably round about a level of 50 μg. of vitamin B_{12}. It has not yet been proved that all the cyanocobalamins require intrinsic factor for their absorption, but suggestions that the vitamin B_{12} conjugates present in liver, or vitamin B_{12} peptides, can be absorbed without intrinsic factor have not yet been substantiated.

Perhaps it would be better to call these different dose levels normal and supernormal rather than physiological and pharmacological, for rabbits normally ingest an amount of vitamin B_{12} which would be supernormal in man. The rabbit obtains its vitamin B_{12} by eating its faeces, particularly the soft faeces which are passed at night and which are especially rich in vitamin B_{12}. The quantity ingested daily represents the equivalent of 500–1,500 μg. or more in man, and the level of vitamin B_{12} in the serum of the rabbit can be as much as 150 times higher than in man (personal communication, Mrs. K. I. Simnett and Dr. G. H. Spray). The vitamin B_{12} in the faeces is produced by the action of bacteria on the food residues. The rabbit, if gifted with speech, would doubtless say that its coprophagy is an example of the process described by Platt and Webb (1946) as the ennoblement of food, and it can hardly be called unphysiological.

The delayed peak in the absorption of physiological doses of vitamin B_{12} is due to temporary storage of the vitamin in the wall of the small intestine. Next it passes into the circulation and is found in more or less equal concentration in the liver, spleen, and kidneys 24 hours after ingestion. There is then redistribution with accumulation of the vitamin in the liver, a phenomenon which is used in Glass's test for the diagnosis of pernicious anaemia (Doscherholmen and Hagen, 1959; Doscherholmen, Finley, and Hagen, 1960). The turnover of vitamin B_{12} is slow, and in long-term experiments only 0.2 to 0.3% of the total amount of radioactive vitamin B_{12} contained in the body is excreted per day. The half-life of a tracer dose in the liver is of the order of twelve months.

Vitamin B_{12} is excreted in the bile, but much of this excreted material is reabsorbed, so that there is a closed enterohepatic circulation (Gräsbeck, Runeberg, and Simons, 1959). A break in this enterohepatic circulation is an important factor in the depletion of the body of vitamin B_{12} in pernicious anaemia and after gastrectomy, because intrinsic factor is needed for the reabsorption of the vitamin B_{12} of the bile. Dr. G. H. Spray and Miss Maureen Booth, working in our laboratory, have found that, whereas normal rats excreted 38% of a parenteral dose of radioactive vitamin B_{12} in the faeces, gastrectomized rats excreted 58%; the excretion returned nearly to normal in the gastrectomized rats when they were given rat gastric juice (personal communication).

Nature of Intrinsic Factor

Intrinsic factor is non-dialysable and easily destroyed by heat. It is inactivated by pepsin and some other proteolytic enzymes, and if gastric juice is to be preserved for study it should be neutralized and then frozen and kept in a deep freeze. The chemical nature of intrinsic factor is not yet known. Concentrates have been obtained of which as little as 0.3 mg. will ensure normal absorption of the dose of radioactive vitamin B_{12} used in the Schilling test or the faecal excretion test in patients with pernicious anaemia, and there is reason to believe that preparations active in a dose of 30 μg. could be obtained (Heatley, Sheikh, and Taylor, 1960). Intrinsic factor concentrates are prepared from the mucoprotein fraction of the gastric juice or mucosa, but it has not been established for certain that intrinsic factor itself is a mucoprotein (Ellenbogen and Williams, 1960).

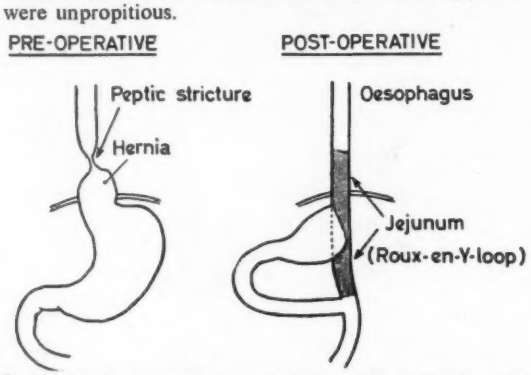
Intrinsic factor was originally studied in human gastric juice, and, though for many purposes it is convenient to use preparations from animal stomachs, these can be misleading, because intrinsic factor from different species may differ in site of production, activity in the same and different species, association with inhibitors, and tendency to produce refractory states. Human gastric juice and most preparations of hog intrinsic factor do not promote the absorption of vitamin B_{12} in the gastrectomized rat, in contrast to homogenates of rat stomach and rat gastric juice. In isolated segments of rat intestine human gastric juice does not increase the uptake of vitamin B_{12} (Abels, 1959). Moreover, it is possible to produce antibodies to intrinsic factor in animals (Taylor and Morton, 1958, 1959).

A number of preparations in which vitamin B_{12} is combined with concentrates of hog intrinsic factor for the oral treatment of pernicious anaemia have proved unsatisfactory and have shown a progressive decline in effect (Blackburn, Cohen, and Wilson, 1955). This loss of effect is due to a diminished ability of the patient to absorb vitamin B_{12} under the influence of hog intrinsic factor (Schwartz, Lous, and Meulengracht, 1958). In patients in whom resistance has occurred it may be overcome by using human intrinsic factor or by giving massive doses of hog intrinsic factor (Berlin, Berlin, Brante, and Sjöberg, 1958). The mechanism underlying this development of resistance is not yet understood. Resistance does not occur on treatment with desiccated whole hog's stomach, and it does not develop with all commercial preparations of hog intrinsic factor (Wilkinson, 1949 ; Ellenbogen, Williams, and Lichtman, 1960).

Mode of Action of Intrinsic Factor

Transport of substances across membranes often requires a carrier which enables the substance to pass through the cell membrane and a receptor which holds it within the cell. This mechanism appears to apply to the absorption of vitamin B_{12}. The concept of the "binding" of vitamin B_{12} was introduced by Ternberg and Eakin (1949). They showed that normal gastric juice contains a component which combines stoichiometrically with vitamin B_{12} to form a complex which is not dialysable or dissociated by dialysis and in which the vitamin B_{12} is no longer available to bacteria. A good deal of confusion has been caused because many naturally occurring substances which do not have intrinsic factor activity can bind vitamin B_{12}. Nevertheless, ability to bind vitamin B_{12} is one of the essential characteristics of intrinsic factor, and the most potent preparations of intrinsic factor so far made have a high binding capacity. Thus it seems clear that the absorption of vitamin B_{12} is related to its binding to intrinsic factor which acts as a carrier.

Normal gastric juice can remove vitamin B_{12} from beef muscle and casein *in vitro*, and this is probably the first step in the absorption of vitamin B_{12} from the food (Cooper and Castle, 1960). The presence of HCl facilitates the binding of intrinsic factor with vitamin B_{12} in the stomach. The necessity for this early binding of vitamin B_{12} is shown by some observations we have made on patients in whom the stomach has been completely bypassed in the treatment of peptic stricture of the oesophagus and the oesophagus joined to a Roux loop of jejunum (Callender, Witts, Allison, and Gunning, 1961) (see Fig.). Although much of the proper gastric gland area was intact and probably secreting, the patients had a gross defect in the absorption of vitamin B_{12} which could be corrected by the addition of intrinsic factor. The probability is that contact between intrinsic factor and vitamin B_{12} was established too late for effective union between them to take place, either because the vitamin B_{12} had already become bound to other substances or because conditions in the jejunum were unpropitious.



By-passing the stomach may produce avitaminosis B_{12} and megalobiastic anaemia even though the stomach itself is intact.

As long ago as 1938 Uotila found that the strength of the antianaemic activity of the dried defatted tissues of the gastro-intestinal tract of the pig appeared to decrease in the order pylorus, ileum, duodenum, jejunum, cardia, colon, and fundus. In modern terms this distribution would be explained on the hypothesis that in the pig intrinsic factor is secreted by the pyloric gland organ, and the complex of intrinsic factor with vitamin B_{12} is absorbed in the ileum. Experiments in the rat suggested that the greatest absorption occurred in the second and third quarters of the small intestine (Reynell, Spray, and Taylor, 1957). In man both clinical observation of patients with resections and direct measurement of the distribution of radioactivity in the small intestine of patients during the absorption of ^{56}Co-labelled vitamin B_{12} indicate that the site of absorption of vitamin B_{12} is the ileum (Booth and Mollin, 1959 ; Allcock, 1961).

The localization of the absorption of vitamin B_{12} is probably determined by the presence of a specific receptor for it (Glass, Boyd, and Stephanson, 1954). We can think of intrinsic factor as an amboceptor with two combining groups, one of which links up with vitamin B_{12} and the other with an acceptor in the cells of the ileum. The acceptor is apparently near the surface of the cell, for, although it can be temporarily saturated with the vitamin B_{12} complex, it quickly clears itself and is ready to accept further vitamin B_{12} long before the previously absorbed vitamin B_{12} has passed into the blood-stream. Moreover, it can be temporarily blocked by intrinsic factor from a different species without promoting the absorption of vitamin B_{12}. The last stage of absorption is the passage of the intramural vitamin B_{12} into the blood-stream, a process which requires time and probably the output of energy by the cell. It appears to be uninfluenced by the concentration of vitamin B_{12} in the blood-stream. Whether the intrinsic factor also enters the blood-stream or is destroyed is not known.

Site of Production of Intrinsic Factor

Shortly after Castle had given his preliminary communication on intrinsic factor at the meeting of

the American Society for Clinical Investigation in Washington in 1928, Sturgis and Isaacs (1929) in America and Wilkinson (1930) in England showed that desiccated stomach also was effective in the treatment of pernicious anaemia. Sturgis and Isaacs used fresh whole hog stomach which was desiccated so that 30 g. of the dried substance was equivalent to 190 g. of the fresh tissue. They believed that its potency was due to an enzymatic action of the intrinsic factor in the mucosa upon the muscular layer.

By cutting wedges of the entire thickness of the stomach—that is, mucous membrane plus muscular layer—from carefully chosen areas of the pig's stomach, Meulengracht (1934) showed that material from the pyloric gland area was highly active, but material from the body or proper gland area was inactive in pernicious anaemia. Preparations from the duodenum of the hog containing Brunner's glands were also active (Meulengracht, 1935). Preparations from the body had a high concentration of pepsin and rennin, while those from the pyloric gland area and the cardia contained very small amounts (Meulengracht and Schiødt, 1934). Hence the production of intrinsic factor is dissociated from that of pepsin and rennin in the pig.

Following on these early studies it has been clearly demonstrated that in the hog both pure pyloric secretion and pure duodenal secretion from the area of Brunner's glands contain intrinsic factor (Landboe-Christensen and Bohn, 1947; Landboe-Christensen and Wandall, 1953; Heatley, Jennings, Florey, Watson, Turnbull, Wakisaka, and Witts (1954). In the pig it is possible to strip the mucosa, together with its muscularis mucosae, from the muscular coat of the stomach (Meulengracht, 1952). Some confusion was caused by the fact that preparations from each of these two layers showed antianaemic activity. The explanation appears to be that the muscular layer always contains traces of intrinsic factor, derived in part from pyloric glandular tissue which has penetrated into the muscular layer and partly from diffusion of intrinsic factor into the muscular layer during the interval of several hours which elapses between killing the pig and making the preparations. The admixture need only be small; Meulengracht (1953) showed that preparations made from 99 parts of hog uterus and one part of pyloric mucosa were active.

It would therefore seem that Sturgis and Isaacs were correct and that the antianaemic action of desiccated hog stomach is due to the interaction of intrinsic factor derived from the pyloric glands with vitamin B_{12} which is present in both the mucosal and the muscular layers. Meulengracht (1939) associated the pyloric glands of the stomach and Brunner's glands of the duodenum together as the pyloric gland organ and suggested that pernicious anaemia was due to disease of this organ.

The hypothesis, though logical, was a disturbing one. Pernicious anaemia only rarely occurs after partial gastrectomy for peptic ulcer in man, though the aim of the surgeon is to eliminate the pyloric antrum; and Meulengracht (1939) himself showed that the pathological changes visible in the human stomach in pernicious anaemia were limited to the proper gastric gland area in the body and did not reach down into the pyloric gland organ. Moreover, Castle, Townsend, and Heath (1930) had produced some evidence that the duodenal juice in man does not contain intrinsic factor, and later work has supported them (Landboe-Christensen and Bohn, 1947).

The next step was the application of Meulengracht's technique to apparently healthy human stomachs obtained at necropsy. Wilkinson, Klein, and Ashford (1938), who used whole stomachs incubated with beef, had already shown that the normal human stomach possessed intrinsic factor activity whereas the stomach of patients with pernicious anaemia did not. Fox and Castle (1942) showed that preparations obtained from the pyloric area in man were probably inactive in the treatment of pernicious anaemia, but preparations from the body and the cardia were fully active. Similar results were obtained by Landboe-Christensen and Plum (1948) and Meulengracht (1952). Further experiments by Landboe-Christensen, Berk, and Castle (1952) showed that preparations from the body of the human stomach possessed antianaemic activity, from the duodenum possessed weak activity, and the jejunum was inactive. The orthodox conclusion from these experiments is that, whereas in the pig intrinsic factor is produced by the pyloric gland organ, in man it is produced in the proper gastric gland area, and any activity demonstrated lower down is due to contamination or reabsorption.

A Technical Difficulty

Much of the early work on pernicious anaemia was marred by the inability or undesirability of submitting a sufficient number of patients with pernicious anaemia in relapse to test, and the result has often been the erection of a large superstructure of theory on an inadequate basis of fact. There are obvious objections to using, for therapeutic trials, human tissues obtained after death, even in these days of artery banks and corneal grafts. Nevertheless, it is wise to remember that in experiments of this type one man is equal only to one mouse, and the experiments reviewed above were insufficient in number and the results were not clear-cut. They were done by the Castle test, which is apt to be vitiated by spontaneous remissions and which has been superseded by the use of tracer doses of radioactive vitamin B_{12} in patients with pernicious anaemia in remission. The preparations from the different parts of the human stomach and intestine were not made as a rule until 12 to 14 hours after death, and during this time intrinsic factor may well have diffused from its place of origin to other parts of the stomach or intestine. The impracticability of getting absolutely fresh material from human necropsies has probably been crucial in blocking this particular line of attack.

Further progress in this field may have to await technical improvements which will allow us to demonstrate intrinsic factor in human biopsy material. One of the difficulties is that there appear to be species differences in intrinsic factor, as already mentioned. Intrinsic factor derived from man or the pig is not effective in the gastrectomized rat, at any rate in crude preparations, while intrinsic factor derived from the rat is effective (Abels, 1959; Castle, 1959; Heatley, Sheikh, and Taylor, 1960). Landboe-Christensen and Hoff-Jörgensen (1955) studied the ability of different portions of the mucosa to bind vitamin B_{12}, obtaining human material from cases of partial gastrectomy. In the pig the highest binding activity was found in the area of the pyloric gland organ, whereas in man the maximum binding activity was found in the body of the stomach. Human duodenal mucosa showed some activity. Unfortunately, ability to bind vitamin B_{12} is not peculiar to intrinsic factor, and the fact that the highest activity found in man was only about 1 or 2% of the maximum

found in the pig makes the localizing value of these experiments doubtful.

Meulengracht (1952) wrote that it would be inexplicable if secretion of the intrinsic factor in one species took place in the pyloric glands and in another species in the fundus glands; in fact, it would shake the foundations of all comparative physiology. The only animal other than man and the pig which has been fully studied is the rat, and here the state of affairs seems to be much the same as in man. In the rat the stomach consists of two parts—a proximal fore-stomach, which is lined by squamous epithelium, and a distal glandular portion. The latter consists of a body or proper gastric gland area and a pyloric area. Removal of the fore-stomach and the proper gastric gland area, leaving the pyloric area *in situ*, greatly reduces the absorption of vitamin B_{12} and indeed has much the same effect as total gastrectomy. Administration of extracts of body mucosa restores absorption to normal but extracts of antrum are ineffective (Keuning, Arends, Mandema, and Nieweg, 1959).

Efforts to locate the site of production of intrinsic factor more closely and to discover the cells by which it is secreted have so far given inconclusive results. On the hypothesis that intrinsic factor is a mucoprotein or mucopolysaccharide, different areas of the stomach have been stained with the periodic-acid–Schiff (P.A.S.) stain, which reacts with polysaccharides. In man and rat the surface epithelium and the mucous neck cells of the body of the stomach give the P.A.S. reaction, but in the pig there is no correlation between the P.A.S. reaction and either antianaemic activity or the binding of vitamin B_{12}.

The blood-group substances are present in high concentration in the mucosa of the stomach and duodenum. They are macromolecules which belong to the class of compounds known as mucopolysaccharides (Morgan and Watkins, 1959). Fluorescent antisera can be prepared from them and used in "staining" or locating the antigen in the tissues. The patterns of staining are complicated and differ in secretors and non-secretors, but the blood-group substances are most easily demonstrated in the superficial cells of the stomach and to a smaller extent in the mucoid cells in the glands. Parietal cells may stain but not zymogenic cells (Glynn, Holborow, and Johnson, 1957). It is possible to concentrate material from gastric juice which has strong intrinsic-factor activity and which is free of blood-group substances, though it is probably not homogeneous material. The fluorescein technique has been employed with this material as the antigen in an attempt to locate the site of origin of intrinsic factor, using fresh human stomachs removed at operation, but apparently the intrinsic factor rapidly diffuses out of the cells, and so far it has not been possible to obtain sharp pictures (Drs. E. J. Holborow and K. B. Taylor, personal communication).

It may well be that the hypothesis that intrinsic factor is a mucoprotein or mucopolysaccharide is an *ignis fatuus* which has misled workers in this field. It is not supported by radioautographic studies which give the most persuasive results to date. In these experiments gastric mucosa from the rat was incubated with solutions of radioactive vitamin B_{12} so that the radioactive vitamin B_{12} might become bound to any intrinsic factor which was present, and the sections were then mounted and developed. The resultant blackening from radioactivity was limited to the mucosa of the body. The mucoid neck cells were completely devoid of radioactivity, which was confined to the deeper portions of the glands and was found exclusively in the chief or zymogenic cells (Keuning *et al.*, 1959). The incompatibility between these observations in the rat and the complete separation of the secretion of intrinsic factor and pepsin in the pig is so great as to make one hesitate about their interpretation.

Present Position of Castle's Hypothesis

This review of more than 30 years' work since Castle's first publications shows that his hypothesis has stood the test of time as a satisfactory explanation of the pathological physiology of pernicious anaemia and has proved fruitful as a basis of research. There is still, however, a large defect in this field of knowledge. We do not yet know the chemical nature and structure of the intrinsic factor or factors, or the site of production, and this remains one of the most important unsolved problems in an area which is of common interest to the haematologist and the gastroenterologist.

Conclusion

The treatment of pernicious anaemia with liver was discovered by Minot and Murphy in 1926. The efficacy of iron in hypochromic anaemia and the appropriate dosage of ferrous and ferric salts were rediscovered about the same date. It might well have been thought that the problems of the deficiency anaemias were solved and clinical scientists should now pass on to other studies. Indeed, many did think so, and my friend Professor S. Alstead will perhaps forgive me for quoting some words he wrote in 1949:

> "The discovery of the liver treatment of pernicious anaemia was not the outcome of logical deduction from physiological premises; and to this extent the discovery comes into the class of happy accidents. Now the effect of this momentous discovery was the releasing of a vast number of workers on the whole subject of blood diseases and the physiology of blood formation. I do not maintain that this great effort has been in vain; but it is remarkable that when research takes on this form it dissipates itself over an enormous field, and any further advance comparable with the original discovery is rare. The researcher's attempts to predict new therapeutic advances from previous discoveries have nearly always proved disappointing. There is a further reason for choosing pernicious anaemia as an illustration. It is a comparatively rare disease; and I feel most strongly that as research-workers we are excessively concerned with the minutiae of uncommon diseases while the common and disabling maladies receive far too little attention."

One need only mention vitamin B_{12}, folic acid, and folic-acid antagonists to realize that the discovery of the therapeutic action of liver was far from exhausting the mine of information to be obtained from the study of pernicious anaemia, even in terms of treatment. But so long as we know only the treatment of a disease our work is but half done. Consider, for example, the life-history of diabetes mellitus, which is hardly yet completely elucidated nearly forty years after the isolation of insulin and which, though modified, has not been fundamentally changed by insulin. The layman

is rightly more interested in prevention than treatment, and for this we must know the aetiology of a disease, which may well prove a complex genetic and environmental problem. And, finally, we must know the mechanism of symptoms. I have said some hard things in my time about phenomenology, but there is no doubt that the study of symptoms may give us power to control disease. A good example is the discovery of chlorothiazide, which would have been unlikely to be made if so many people had not been fascinated by the study of the symptom, oedema.

A disease is nature's experiment. I have compared it with a mine, a gold mine, for example, in which uranium is found by chance by men who seek for gold. I have also compared it, on another occasion, with the quinine molecule, which has preoccupied the German chemists and their successors since 1856, when W. H. Perkin, in attempting to prepare quinine from aniline, almost by accident discovered a new world of colour in the aniline dyes. Antipyrine and plasmoquine came directly from the study of the quinine molecule, and indirectly it was an inspiration in the search for chemical remedies for infectious disease which was to prove so successful in our time.

Finally, one can compare a disease like pernicious anaemia with a machine-tool. Although gastroenterology has advanced greatly on the observational side, it is still a laggard so far as the understanding and prevention of disease are concerned. To support this statement I need only recall how ineffective we are in the prevention and treatment of peptic ulcer, cancer of the stomach, regional ileitis, and ulcerative colitis. Clinical scientists, working on the anaemias, have forged new tools for the study of disturbances of the gastrointestinal tract which have made this one of the foci of medical progress. It would probably be true to say that as much, or more, is known about the mechanism of absorption of vitamin B_{12} by the cells of the intestine as of that of any other food principle and that a new salient of knowledge has been opened by the studies of pernicious anaemia which I have been discussing in this lecture.

REFERENCES

Abels, J. (1959). *Instrinsic factor van Castle en resorptie van vitamine B_{12}*. V.R.B., Groningen.
Ackroyd, J. F. (1949). *Clin. Sci.*, **7**, 249.
—— (1955). *Brit. med. Bull.*, **11**, 28.
Allcock, E. (1961). *Gastroenterology*, **40**, 81.
Alstead, S. (1949). *Lancet*, **1**, 171.
Ashby, W. (1919). *J. exp. Med.*, **29**, 267.
Asher, R. (1959). *Lancet*, **2**, 417.
Aufderheide, A. C. (1960). *Amer. J. clin. Path.*, **34**, 258.
Badenoch, J. (1960). *Brit. med. J.*, **2**, 879, 963.
Bailey, N. T. J. (1957). *The Mathematical Theory of Epidemics*. Griffin, London.
Baldini, M., and Pannacciulli, I. (1960). *Blood*, **15**, 614.
Belcher, E. H., and Hughes Jones, N. C. (1960). *Clin. Sci.*, **19**, 657.
Berlin, N. I., Waldmann, T. A., and Weissman, S. M. (1959). *Physiol. Rev.*, **39**, 577.
Berlin, R., Berlin, H., Brante, G., and Sjöberg, S.-G. (1958). *Acta med. scand.*, **162**, 317.
Beutler, E., Drennan, W., and Block, M. (1954). *J. Lab. clin. Med.*, **43**, 427.
Blackburn, E. K., Cohen, H., and Wilson, G. M. (1955). *Brit. med. J.*, **2**, 461.
Bomford, R. R. (1946). Ibid., **2**, 996.
Booth, C. C., and Mollin, D. L. (1959). *Lancet*, **1**, 18.
Bothwell, T. H., Callender, S., Mallett, B., and Witts, L. J. (1956). *Brit. J. Haematol.*, **2**, 1.
—— Hurtado, A. V., Donohue, D. M., and Finch, C. A. (1957). *Blood*, **12**, 409.
Broquist, H. P. (1956). *J. Amer. chem. Soc.*, **78**, 6205.
Brown, G. M., Hayward, O. C., Powell, E. O., and Witts, L. J. (1944). *J. Path. Bact.*, **56**, 81.
Callender, S. T., Retief, F. P., and Witts, L. J. (1960). *Gut*, **1**, 326.
—— Witts, L. J., Allison, P. R., and Gunning, A. (1961). Ibid., **2**, 150.
Cameron, D. G., Watson, G. M., and Witts, L. J. (1949). *Blood*, **4**, 793, 803.
Castle, W. B. (1959). *Gastroenterology*, **37**, 377.
—— Townsend, W. C., and Heath, C. W. (1930). *Amer. J. med. Sci.*, **180**, 305.
Chanarin, I., Dacie, J. V., and Mollin, D. L. (1959). *Brit. J. Haematol.*, **5**, 245.
Coombs, R. R. A., Mourant, A. E., and Race, R. R. (1945). *Brit. exp. Path.*, **26**, 255.
Cooper, B. A., and Castle, W. B. (1960). *J. clin. Invest.*, **39**, 199.
Dacie, J. V. (1960). *The Haemolytic Anaemias*, 2nd ed., vol. 1. Churchill, London.
—— Smith, M. D., White, J. C., and Mollin, D. L. (1959). *Brit. J. Haematol.*, **5**, 56.
Doscherholmen, A., Finley, P. R., and Hagen, P. S. (1960). *J. Lab. clin. Med.*, **56**, 547.
—— and Hagen, P. S. (1959). Ibid., **54**, 434.
Ellenbogen, L., and Williams, W. L. (1960). *Biochem. biophys. Res. Comm.*, **2**, 340.
—— —— and Lichtman, H. C. (1960). *Brit. med. J.*, **2**, 1066.
Evans, R. S., Takahashi, K., Duane, R. T., Payne, R., and Liu, C.-K. (1951). *Arch. intern. Med.*, **87**, 48.
Faber, K. (1895). *Hospitalstidende*, **38**, 601.
Finch, C. A., Coleman, D. H., Motulsky, A. G., Donohue, D. M., and Reiff, R. H. (1956). *Blood*, **11**, 807.
Fox, H. J., and Castle, W. B. (1942). *Amer. J. med. Sci.*, **203**, 18.
Giblett, E. R., Coleman, D. H., Pirzio-Biroli, G., Donohue, D. M., Motulsky, A. G., and Finch, C. A. (1956). *Blood*, **11**, 291.
Girdwood, R. H. (1953). *Lancet*, **2**, 53.
—— (1960). *Advanc. clin. Chem.*, **3**, 235.
Glass, G. B. J., Boyd, L. J., and Stephanson, L. (1954). *Science*, **120**, 74.
Glynn, L. E., Holborow, E. J., and Johnson, G. D. (1957). *Lancet*, **2**, 1083.
Gordon, A. S. (1959). *Physiol. Rev.*, **39**, 1.
Gräsbeck, R. (1960). *Advanc. clin Chem.*, **3**, 299.
—— Runeberg, L., and Simons, K. (1959). *Acta physiol. scand.*, **47**, 370.
Grinstein, M., Bannerman, R. M., Vavra, J. D., and Moore, C. V. (1960). *Amer. J. Med.*, **29**, 18.
Harrington, W. J., Minnich, V., Hollingsworth, J. W., and Moore, C. V. (1951). *J. Lab. clin. Med.*, **38**, 1.
Heatley, N. G., Jennings, M. A., Florey, H., Watson, G. M., Turnbull, A., Wakisaka, G., and Witts, L. J. (1954). *Lancet*, **2**, 578.
—— Sheikh, M. A., and Taylor, K. B. (1960). *Biochem. J.*, **76**, 342.
Heilmeyer, L. (1959). *Dtsch. med. Wschr.*, **84**, 1761.
Herbert, V. (1961). *J. clin. Invest.*, **40**, 81.
Huff, R. L., Hennessy, T. G., Austin, R. E., Garcia, J. F., Roberts, B. M., and Lawrence, J. H. (1950). Ibid., **29**, 1041.
Johns, D. G., Sperti, S., and Burgen, A. S. V. (1961). *Canad. med. Ass. J.*, **84**, 77
Keuning, F. J., Arends, A., Mandema, E., and Nieweg, H. O. (1959). *J. Lab. clin. Med.*, **53**, 127.
Knowles, J. P., Prankerd, T. A. J., and Westall, R. G. (1960). *Lancet*, **2**, 347.
Lajtha, L. G., and Oliver, R. (1960). *Ciba Foundation Symposium on Haemopoiesis*, edited by G. E. W. Wolstenholme and M. O'Connor, p. 289. Churchill, London.
Landboe-Christensen, E., Berk, L., and Castle, W. B. (1952). *Amer. J. med. Sci.*, **224**, 1.
—— and Bohn, C. L. S. (1947). *Acta med. scand.*, **127**, 116.
—— and Hoff-Jörgensen, E. (1955). *Acta path. microbiol. scand.*, Suppl. 105, p. 104.
—— and Plum, C. M. (1948). *Amer. J. med. Sci.*, **215**, 17.
—— and Wandall, H. H. (1953). *Acta med. scand.*, **144**, 467.
London, I. M., and West, R. (1950). *J. biol. Chem.*, **184**, 359.
Meulengracht, E. (1934). *Acta med. scand.*, **82**, 352.
—— (1935). Ibid., **85**, 79.
—— (1939). *Amer. J. med. Sci.*, **197**, 201.
—— (1952). *Acta med. scand.*, **143**, 207.
—— (1953). Ibid., **144**, 290.
—— and Schiødt, E. (1934). Ibid., **82**, 375.
Minot, G. R., and Murphy, W. P. (1926). *J. Amer. med. Ass.*, **87**, 470.
Moeschlin, S. (1958). In *Sensitivity Reactions to Drugs*, edited by M. L. Rosenheim and R. Moulton, p. 77. Blackwell, Oxford.
Mollison, P. L. (1956). *Blood Transfusion in Clinical Medicine*, 2nd ed., p. 170. Blackwell, Oxford.
Morgan, W. T. J., and Watkins, Winifred M. (1959). *Brit. med. Bull.*, **15**, 109.
Paulson, M., and Harvey, J. C. (1954). *J. Amer. med. Ass.*, **156**, 1556.
Platt, B. S., and Webb, R. A. (1946). *Proc. Nutr. Soc.*, **4**, 132.
Polland, W. S. (1933). *Arch. intern. Med.*, **51**, 903.
Pollycove, M. (1959). In *Eisenstoffwechsel*, edited by W. Keiderling, p. 20. Thieme, Stuttgart.

Rasch, C. A., Cotton, E. K., Griggs, R. C., and Harris, J. W. (1958). *J. Lab. clin. Med.*, **52**, 938.
Reynell, P. C., Spray, G. H., and Taylor, K. B. (1957). *Clin. Sci.*, **16**, 663.
Salera, U., Tamburino, G., and Magnanelli, P. (1957). *Sci. med. ital.*, **6**, 179.
Schiødt, E. (1938). *Acta med. scand.*, **95**, 49.
Schwartz, M., Lous, P., and Meulengracht, E. (1958). *Lancet*, **2**, 1200.
Sheehy, T. W., Rubini, M. E., Baco-Dapena, R., and Perez-Santiago, E. (1960). *Blood*, **15**, 761.
Shemin, D., and Rittenberg, D. (1946). *J. biol. Chem.*, **166**, 627.
Silverman, M., Gardiner, R. C., and Condit, P. T. (1958). *J. Nat. Cancer Inst.*, **20**, 71.
Spray, G. H., Fourman, P., and Witts, L. J. (1951). *Brit. med. J.*, **2**, 202.
—— and Witts, L. J. (1953). *Clin Sci.*, **12**, 391.
—— —— (1959). *Lancet*, **2**, 702.
Stohlman, F. (1959). *The Kinetics of Cellular Proliferation*, p. 318. Grune and Stratton, New York and London.
Sturgis, C. C., and Isaacs, R. (1929). *J. Amer. med. Ass.*, **93**, 747.
Taylor, K. B., and Morton, J. A. (1958). *Lancet*, **1**, 29.
—— —— (1959). *J. Path. Bact.*, **77**, 117.
Ternberg, J. L., and Eakin, R. E. (1949). *J. Amer. chem. Soc.*, **71**, 3858.
Uotila, U. (1938). *Acta med. scand.*, **95**, 415.
Verloop, M. C., Wolk, M. van der, and Heier, A. J. (1960). *Blood*, **15**, 791.
Watson, G. M., and Florey, H. W. (1955). *Brit. J. exp. Path.*, **36**, 479.
Wilkinson, J. F. (1930). *Brit. med. J.*, **1**, 236.
—— (1949). *Lancet*, **1**, 249, 291, 336.
—— Klein, L., and Ashford, C. A. (1938). *Quart. J. Med.*, **31**, 555.
Witts, L. J. (1932). *Lancet*, **1**, 495.
—— (1950). *Irish J. med. Sci.*, **6**, 315.
—— (1956). *Anaemia and the Alimentary Tract*. Royal College of Physicians, Edinburgh.
—— (1959). *Canad. med. Serv. J.*, **15**, 645.
—— (1960). *Acta haemat (Basel)*, **24**, 1.

GUANETHIDINE IN TREATMENT OF HYPERTENSION

BY

G. E. BAUER, M.R.C.P.

F. J. T. CROLL, M.R.A.C.P.

R. B. GOLDRICK, M.B., B.S.

D. JEREMY, M.R.A.C.P.

J. RAFTOS, M.R.A.C.P.

H. M. WHYTE, M.R.C.P.

AND

A. A. YOUNG, M.R.A.C.P.

From the Cardiovascular Clinic, Sydney Hospital

Effective blood-pressure control in severe hypertension was first made possible with the introduction of hexamethonium by Paton and Zaimis in 1948. The impetus to this discovery came from our surgical colleagues, who during the preceding two decades had shown that ablation of part of the sympathetic nervous system resulted, in some instances, in remarkable falls in blood-pressure. Hexamethonium, the first ganglion-blocking agent of practical value, was succeeded by pentolinium, chlorisondamine, mecamylamine, and pempidine, the introduction of each of these compounds representing an advance in therapy, particularly in respect to improved gastro-intestinal absorption, more uniform blood-pressure control, and some diminution in side-effects.

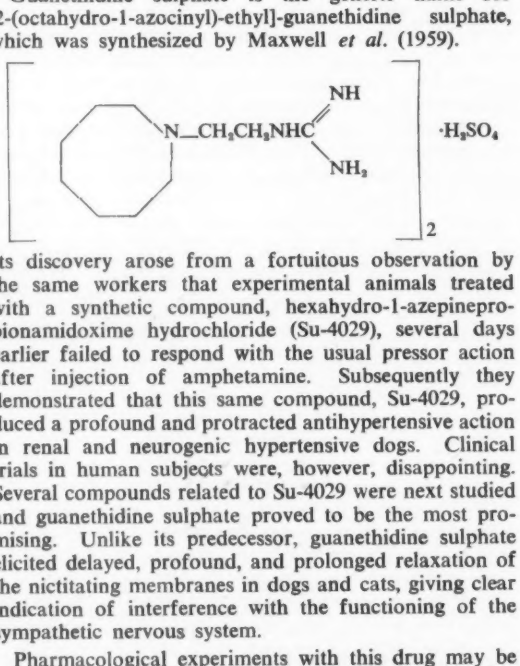
Ganglion-blocking therapy with these drugs was accompanied, when given in adequate therapeutic doses, by symptoms of parasympathetic blockade such as blurred vision, dryness of the mouth, severe gastro-intestinal disturbances, difficulty in micturition, and impotence. These pharmacological side-effects were largely responsible for restricting treatment with these drugs to the severest types of hypertension.

Great strides were made in 1959 with the synthesis of two new compounds which for the first time made good postural blood-pressure control, with selective sympathetic inhibition and without parasympathetic inhibition, a practical proposition. Bretylium tosylate was introduced in Great Britain by Boura *et al.* (1959), and has since been evaluated in many different parts of the world. Guanethidine sulphate, the second compound and the subject of this communication, has been available for a comparable period of time and has been shown to differ from bretylium in a number of important aspects.

It has been our custom at the cardiovascular clinic, Sydney Hospital, to report experiences with new ganglion-blocking agents such as pentolinium (Bauer, 1955), chlorisondamine (Bauer *et al.*, 1957), mecamylamine (Bauer *et al.*, 1959), pempidine (Croll *et al.*, 1961), and bretylium (Bauer, 1961). We now wish to record our impressions of guanethidine after treating 28 patients for a period of up to 12 months.

Pharmacology

Guanethidine sulphate is the generic name for [2-(octahydro-1-azocinyl)-ethyl]-guanethidine sulphate, which was synthesized by Maxwell *et al.* (1959).



Its discovery arose from a fortuitous observation by the same workers that experimental animals treated with a synthetic compound, hexahydro-1-azepinepropionamidoxime hydrochloride (Su-4029), several days earlier failed to respond with the usual pressor action after injection of amphetamine. Subsequently they demonstrated that this same compound, Su-4029, produced a profound and protracted antihypertensive action in renal and neurogenic hypertensive dogs. Clinical trials in human subjects were, however, disappointing. Several compounds related to Su-4029 were next studied and guanethidine sulphate proved to be the most promising. Unlike its predecessor, guanethidine sulphate elicited delayed, profound, and prolonged relaxation of the nictitating membranes in dogs and cats, giving clear indication of interference with the functioning of the sympathetic nervous system.

Pharmacological experiments with this drug may be summarized as follows. (1) Coupled with the relaxant action of the nictitating membrane, guanethidine exerts a marked and prolonged antihypertensive action in unanaesthetized renal and neurogenic hypertensive dogs. (2) Preganglionic stimulation of efferent sympathetic nerves in animals treated with guanethidine fails to elicit normal responses from smooth-muscle effectors, indicating blockade somewhere in the efferent sympathetic nerve–smooth-muscle effector complex. (3) Guanethidine does not suppress but rather augments the response of the effector organs to injected noradrenaline, suggesting that the blocking action is exerted within the nerve and not within the smooth muscle. Patients with hypertension due to phaeochromocytoma may develop a marked pressor response to guanethidine.

(4) Conduction along the pre- and post-ganglionic fibres and transmission across the superior cervical ganglion are only very transiently interrupted by guanethidine.

It was therefore assumed that guanethidine acts at the neuromuscular junction of the sympathetic portion of the autonomic nervous system, interfering with metabolism of a chemical transmitter substance. In addition to suppression of catecholamine release from post-ganglionic sympathetic nerve fibres, it has been shown to induce depletion of endogenous catecholamine stores in tissues such as blood-vessels and heart. Sheppard and Zimmerman (1959) demonstrated a 40% reduction of catecholamine concentration after guanethidine administration, and in this way its behaviour is comparable to that of reserpine.

Pharmacological observations on eight hypertensive human subjects were reported by Barnett *et al.* (1960). Reduced reflex sympathetic activity, as judged by the presence of exaggerated postural hypotension, impaired cardio-accelerator and pressor responses to exercise, reduced cold pressor response, and absence of sweating after indirect heating, was observed in all subjects, but in none of the human experiments were sympathetic reflexes completely blocked. No consistent effect on the parasympathetic nervous system was demonstrated; guanethidine did not seem to modify slowing of the heart rate after carotid sinus pressure, nor did it interfere with the cardio-accelerator effect of atropine.

Absorption, distribution, and excretion of the drug were studied by Dollery *et al.* (1960), using radioactive guanethidine labelled with ^{14}C in the guanidine carbon. Incomplete gastro-intestinal absorption was demonstrated by the finding of a total 24-hour urinary excretion of only 20% after an oral dose compared with a 50% excretion after an intravenous dose. After oral treatment a considerable quantity of guanethidine was recovered from the faeces.

One of the important characteristics of guanethidine is its prolonged and cumulative effect. Urinary excretion after an oral dose was low in the first two hours, then rose to a maximum betwen two and four hours after ingestion, and appreciable urinary excretion was found even after 72 hours. Clinical studies demonstrated even more gradual onset of drug action and long-sustained hypotensive effect. With relatively large initial doses of guanethidine, such as 100 mg. daily, no significant blood-pressure reduction could be demonstrated in the first four days of treatment, and similarly after cessation of treatment blood-pressure rose gradually over seven days to pretreatment levels. This "hang-over" of drug-effect is particularly noticeable in the presence of impaired renal function and after prolonged periods of treatment with high doses.

Subjects

Since January, 1960, 28 patients (20 men, 8 women) suffering from hypertension have been treated with guanethidine for a period of up to 12 months (see Table). Their ages ranged from 29 to 61 years. All patients were fully investigated in order to establish a cause for their hypertension and also to determine the extent of cardiac, renal, and vascular damage. In addition to a detailed history and full physical examination, all patients had a careful ophthalmoscopic inspection, urinalysis including microscopy, estimation of blood urea nitrogen, electrocardiography, and chest *x*-ray examination. Further renal function tests, including intravenous pyelography and renal aorto-

Details of Cases

Case No.	Sex and Age	Diagnosis	Initial Blood-pressure (mm. Hg)	Fundi	E.C.G.	Blood urea Nitrogen (mg./100 ml.)	Complications	Treatment			Blood-pressure Control	Side-effects	Cessation of Treatment
								Daily Dose (mg.)	Duration in Months	Additional Treatment			
1	M 49	Ess.Hyp.	210/150	4	1	16		70	12	H'chlor	Good		
2	F 46	Ren.Hyp.	220/140	2	2	19		40	10	,,	,,	Hypo., Dep.	
3	F 48	Ess.Hyp.	240/120	1	1	17		50	9		Fair	Dia.	
4	M 57	Ren.Hyp.	240/140	4	3	16	Cardiac pain	40	8	H'chlor.	,,	Hypol	
5	F 47	,,	230/130	1	3	17	C.V.A.	20	8	Res.	Good	Hypo.	
6	M 49	Ess.Hyp.	260/150	3	3	19		60	7	H'chlor., Res.	Poor	Dep.	Mental hospital
7	M 58	Ess.Hyp.	240/140	2	3	28	Cardiac pain	75	7	H'chlor.	Fair	Hypo., N.St., Dia.	
8	M 55	Ren.Hyp.	190/120	1	3	14		15	7	H'chlor., Res.	Good	N.St.	
9	F 61	Ess.Hyp.	200/110	1	3	21	Hyp.H.F.	50	6	H'chlor.	Fair	Bradyc.,N.St.	
10	M 55	Ess.Hyp.	240/140	1	1	17		50	6	H'chlor.	Good		
11	F 50	Ren.Hyp.	230/160	3	3	46	Cardiac pain	30	6	Res.	Fair	Hypo.	
12	M 52	Ren.Hyp.	210/130	1	3	19	C.V.A.	37·5	6	H'chlor.	Good	Hypo., N.St.	
13	F 52	Ess.Hyp.	260/130	1	0	11		12·5	6	H'chlor., Res.	,,	N.St.	
14	M 57	Ess.Hyp.	210/110	1	2	22	,,	12·5	5	,,	,,		
15	M 49	Ren.Hyp.	210/120	1	2	16		37·5	2	H'chlor.	Fair	Dia., Dep.	Suicide
16	F 57	Ess.Hyp.	240/130	2	3	17	C.V.A.	50	4	Res.	,,	Hypo., Dia., N. St.	
17	M 29	Ess.Hyp.	240/160	4	0	32		12·5	4	Chlor.	Good	Hypo.	
18	M 42	Ess.Hyp.	240/140	2	3	28		50	4	H'chlor.	,,	Hypo., N.St.	
19	M 58	Ess.Hyp.	230/130	2	1	20	Myoc.Inf.	50	3	Chlor.	,,	Hypo., Dia., F.Ej.	
20	M 48	Ess.Hyp.	200/140	3	1	18	C.V.A.	20	3		,,	Dia.	
21	F 43	Tox.Hyp.	230/150	1	3	13		30	3	Chlor., Res.	,,	N.St.	
22	M 61	Ess.Hyp.	190/100	2	1	15	Cardiac pain C.V.A.	25	3	H'chlor.	,,	Hypo., N.St.	
23	M 52	Ess.Hyp.	210/110	1	1	11		12·5	3	H'chlor.	Poor	Dep.	Overseas
24	M 40	Ren.Hyp.	220/140	2	1	14		40	2		Fair		
25	M 51	Ess.Hyp.	230/140	3	1	23	C.V.A.	20	2	Chlor., Res.	Good		
26	M 55	R.A.St.	210/150	4	2	25	Myco.Inf. Hyp.H.F.	25	2		,,	Hypo.	
27	M 55	Ren.Hyp.	190/110	2	3	30	Cardiac pain	25	2	H'chlor., Res.	,,		
28	M 47	Ess.Hyp.	170/110	1	0	22		12·5	2	H'chlor.	,,		

Bradyc.=Bradycardia. Chlor.=Chlorothiazide. C.V.A.=Cerebrovascular accident. Dia.=Diarrhoea. Dep.=Depression. Ess.Hyp.=Essential hypertension. F.Ej.=Failure of ejaculation. Hypo.=Hypotension. H'chlor.=Hydrochlorothiazide. Hyp.H.F.=Hypertensive heart failure. Myoc.Inf.=Myocardial infarction. N.St.=Nasal stuffiness. R.A.St.=Renal artery stenosis. Res.=Reserpine. Ren.Hyp.=Renal hypertension (chronic glomerulonephritis, chronic pyelonephritis). Tox.Hyp.=Toxaemia hypertension.

graphy, were done when necessary, and tests to exclude phaeochromocytoma or aldosterone-secreting tumour were also carried out when indicated.

As a result of the above investigations nine patients were thought to suffer from chronic pyelonephritis or glomerulonephritis, one patient from post-toxaemia hypertension, and in one patient significant narrowing of a renal artery was demonstrated on aortography. In 17 patients no cause was demonstrated and they were labelled essential or primary hypertension.

Fifteen patients gave a definite family history of hypertension, or other significant vascular disease; this was almost as common in those with renal hypertension as in those with so-called essential hypertension. In 11 patients hypertension was known to have been present for over 10 years, and in a further eight patients for at least five years.

In accordance with criteria for treatment previously outlined, only the severer grades of hypertensive patients were included in this series. The pretreatment diastolic blood-pressure of all subjects, measured at the disappearance of sound, was over 100 mm. of mercury. In six the diastolic blood-pressure was very high, 150 mm. or more of mercury, and in a further 13 it was 130 mm. or more of mercury.

Eight patients had advanced ocular fundal changes with grade III and IV retinopathy (Keith *et al.*, 1939); four of these had frank bilateral papilloedema, the hallmark of malignant hypertension.

Renal function was regarded as impaired in 12 patients. In four there was significant non-protein nitrogen retention with blood urea nitrogen levels between 26 and 44 mg./100 ml., while in a further eight persistent proteinuria was taken as evidence of renal damage.

Cardiac involvement was present in most patients. Left ventricular hypertrophy, as determined by electrocardiography according to criteria previously published, was noted in all but three subjects, the changes being classified as grade III with tall R waves, S-T segment depression, and T-wave inversion in left ventricular surface leads in 12 instances. Of the three patients with normal electrocardiograms, one (Case 17) suffered from a florid malignant hypertension of relatively recent onset. Two patients had suffered from myocardial infarction, a further seven gave a history typical of ischaemic effort pain, and two had been in frank hypertensive heart failure.

Six patients had suffered from cerebrovascular accidents some time before starting guanethidine therapy.

Of the 28 patients, 23 have had prior antihypertensive therapy. Seven patients, six of whom were included in our published trial, had been given bretylium, and in each instance that drug had been stopped on account of increasing tolerance or marked side-effects. Other ganglion-blocking drugs previously used in these patients included pentolinium in seven cases, chlorisondamine in five, mecamylamine in nine, and pempidine in two. Furthermore, 16 patients had had reserpine or a similar rauwolfia preparation and 13 had had chlorothiazide or one of its derivatives, usually as an adjuvant to one of the other drugs.

Patients satisfactorily stabilized on a particular regime were not changed to guanethidine unless side-effects were severe enough to make life miserable.

Compared with our previous series, there has been a subtle change in our clinical material towards a more chronic form of hypertension. The average age of our present patients is slightly higher, and there is a greater incidence of cardiac and cerebral vascular complications but a somewhat lower incidence of advanced retinal changes and renal impairment. The pharmacological properties of the drug, especially its prolonged and cumulative action, made out-patient stabilization relatively simple. This, together with the lower incidence of side-effects, has widened the scope of antihypertensive treatment, and probably explains the difference in patient-material. It is important to bear this fact in mind when comparing the results of our various trials.

Technique of Treatment

Most cases were treated as out-patients even during the initial stabilization period. All were fully informed of the essential properties of guanethidine. They were taught to recognize hypotensive symptoms and warned of the circumstances under which these were particularly likely to occur. No dietary restrictions were imposed except when indicated by the presence of obesity or heart or renal failure.

Guanethidine was made available in 10- and 25-mg. tablets. When blood-pressure reduction was not regarded as an urgent measure we began with 10 or 12.5 mg. once a day at breakfast-time. Out-patients were seen at weekly intervals at the cardio-vascular clinic, when the blood-pressure was measured several times during the morning in the standing position and at least once lying down. Owing to the prolonged and cumulative drug action much less diurnal variation was found when compared with previous ganglion-blocking agents and with bretylium. Adequacy of a given dose of guanethidine could thus be estimated with fewer blood-pressure readings, and this made out-patient supervision easier.

Dosage was increased by 12.5-mg. increments at weekly intervals until an adequate response, judged by standing blood-pressure readings, was obtained. This stage was usually accompanied by the appearance of hypotensive symptoms, especially early in the morning.

More difficulty was experienced in some patients whose treatment began in hospital. Attempts to increase the drug more often than once, or at the most twice a week, when approaching a therapeutic dose, almost invariably led to severe and prolonged hypotensive symptoms necessitating interruption in treatment. It is one of the striking characteristics of guanethidine, as compared with previous available potent hypotensive drugs, that it is more suitable for gradual out-patient stabilization and is hardly to be recommended when blood-pressure reduction is urgent.

The hypotensive effect of guanethidine is greatly potentiated by saluretic agents. The majority of patients in this series were given chlorothiazide 500 mg. twice a day or, more recently, hydrochlorothiazide 25 mg. twice a day. Other hypotensive agents occasionally prescribed included reserpine or a similar rauwolfia preparation. This was advised for those showing a very marked postural difference in blood-pressure in an attempt to obtain some control also in the lying-down position. Except in a few instances the dose of reserpine was kept below or not greater than 0.5 mg. a day.

Results

Blood-pressure Control

Of the 28 patients started on guanethidine, 25 are continuing with treatment. One patient committed suicide while taking the drug, one is at present in a mental hospital being treated for depression, and one interrupted treatment before being adequately stabilized on account of an overseas trip.

Blood-pressure reduction has been achieved in all patients at present under treatment. In 18 blood-pressure control was regarded as good, with standing figures of below 150 mm. Hg systolic and 100 mm. Hg diastolic during a large part of the day. In the remaining seven blood-pressure control was regarded as only fair, which meant a significant reduction but not reaching the figures of 150 and 100 mm.

The dosage of guanethidine which we have found necessary to obtain these results has on the whole been smaller than reported in the literature. Sixteen of our patients were stabilized on 25 to 50 mg. of guanethidine a day, the maximum dose used in this series being 75 mg. a day. We should have no hesitation in exceeding this dosage, but so far have not had need to.

Five patients obtained adequate blood-pressure reduction with 12.5 mg. a day. Four of these were relatively mild cases with grade I or II retinopathy and normal renal function; they all received additional hydrochlorothiazide and two of them also reserpine. The fifth patient (Case 17) suffered from severe malignant hypertension and renal damage. He was initially stabilized in hospital on a daily dose of 50 mg. After discharge from hospital he developed severe morning hypotension and gradually the dose of guanethidine was reduced to 12.5 mg. with good blood-pressure control. He has now continued on this regime for over three months with excellent clearing of papilloedema, and has been able to resume his normal work.

Twenty-three patients received some additional hypotensive treatment. Sixteen were given hydrochlorothiazide and four chlorothiazide in dosage mentioned above. Ten patients were also given reserpine or a similar rauwolfia preparation, often in conjunction with a saluretic agent.

Hypotensive Symptoms

Hypotensive symptoms were mentioned by 13 patients, most of them receiving larger doses of guanethidine. Nine of the 13 were taking 37.5 mg. a day or more, but one complained of hypotensive symptoms on as little as 20 mg. guanethidine a day.

Hypotensive symptoms appeared mainly under four sets of circumstances. On occasion more than one factor was evidently contributory. First of all there was the well-known postural hypotension, patients feeling giddy and somewhat nauseated when standing still for any length of time or when suddenly getting up from the reclining posture. Secondly, there was the hypotension associated with augmented drug-action caused by hot weather, excessive perspiration, marked diuresis, gastro-enteritis, and other forms of sodium loss. The third form of hypotension is confined to the early hours of the morning, and appears to be peculiar to guanethidine and its prolonged and cumulative effect. This morning hypotension takes the form of marked fatigue and tiredness, lack of energy, and muscle weakness, and lasts an hour or two after awakening. It occurs before the day's dose of guanethidine is taken, and thus results from a cumulative effect of the previous day. Attempts to modify and reduce the incidence and severity of this morning hypotension by dividing the daily dose of guanethidine or by administering the drug at some later time during the day have been unsuccessful. Unless it is possible to encourage a patient to accept it as a reasonable price for adequate blood-pressure control, the only remedy is reduction in the dose of guanethidine, and thus risking loss of good control.

A fourth type of hypotension is that following exertion which takes the form of fatigue and dyspnoea, especially during morning hours. It has previously been noted with bretylium and occasionally reported with older ganglion-blocking agents. Dollery *et al.* have issued the warning that it is inadvisable to dismiss as neurotic patients' complaints of faintness and weakness, even in the face of high-standing blood-pressures, without measuring the blood-pressure immediately after exercise. We have repeatedly observed the tendency for the blood-pressure to be much lower after a brisk walk or climbing stairs in patients receiving adequate doses of guanethidine.

Side-effects

A number of side-effects other than hypotension were noted during the follow-up period. Most of them appeared to be the result of sympathetic inhibition and unopposed parasympathetic action, and resembled those observed with bretylium and to a minor extent with reserpine. Effects of parasympathetic blockade, for so long the bugbear of ganglion-blocking therapy, were conspicuous only by their absence.

A tendency to diarrhoea was reported by seven patients. This largely took the form of a sudden urge to defaecate, usually in the morning hours, perhaps repeated once or twice, rather than true diarrhoea with very frequent watery motions. This "intestinal hurry" was uncommon in patients taking a small dose of guanethidine and was observed only once, in a transient form, in patients taking 25 mg. or less. The severer forms of this disturbance are usually controllable by a belladonna or bismuth and opium mixture or by one of the synthetic parasympathetic inhibitors such as propantheline bromide. A small dose of ganglion-blocking agent such as mecamylamine or pempidine should also control this side-effect.

Nasal stuffiness was noted by nine patients. It was rarely of great consequence, and often was elicited only by specific questioning. Nose-drops proved of little symptomatic help. Some patients complained of soreness of the eyes associated with conjunctival injection, Parotid-pain, a common side-effect with bretylium, was not complained of by any patient in this series although it has been reported by other authors. The effect on sexual function in the male was similar to that observed with bretylium and comparable to that after lumbar sympathectomy. In contrast with ganglion-blocking drugs there was no interference with potency; erection and orgasm occurred normally but seminal ejaculation was absent or much reduced. Occasionally frequency of micturition was observed by patients.

Guanethidine frequently slowed the heart rate. One patient (Case 9), who had suffered from hypertensive heart failure and had been treated with digitalis and diuretics for years, was noted, six months after the beginning of guanethidine therapy, to have a slow

irregular pulse of 35 beats a minute. Electrocardiograms confirmed that the arrhythmia was due to sinus bradycardia with nodal escape. The bradycardic effect of guanethidine is particularly pronounced in patients receiving digitalis and diuretics, and extra care in supervision is advisable under these circumstances.

Four patients developed depressive symptoms during the period of observation. One patient (Case 15) with cyclothymic temperament committed suicide. He had previously developed reserpine depression and was under psychiatric supervision throughout. Ten weeks after the starting of guanethidine treatment and while taking 37.5 mg. of this drug daily in conjunction with hydrochlorothiazide, he was found dead in his factory. A definite worsening of his depression had been noted when last seen a week before his death, and after consultation with the psychiatrist he was urged to accept institutional treatment, which he refused.

Another patient (Case 6) who had previously been treated with electric convulsion therapy for depression is at present receiving psychiatric in-patient treatment. He had proved a difficult patient, unable to be satisfactorily controlled with bretylium and other hypotensive agents. At the time of his admission to the mental hospital he was taking 60 mg. of guanethidine and 0.25 mg. of reserpine a day. It is difficult to estimate to what extent either or both these drugs contributed to his present depressive state.

Two other patients (Cases 2 and 23) complained of depressive symptoms. The latter, a highly intelligent business executive, while taking as little as 12.5 mg. of guanethidine, complained that he had lost his sense of humour, had become irritable and intolerant both in his business and at home. Hypotensive treatment was interrupted shortly thereafter on account of a proposed overseas trip. Forty-eight hours after cessation of guanethidine treatment the depressive symptoms disappeared, described by the patient as "the lifting of a heavy cloud." In retrospect this patient volunteered the statement that these guanethidine side-effects were rather similar to those experienced when taking reserpine some years earlier.

Discussion

Favourable clinical reports on the use of guanethidine in the treatment of hypertension have been published by Page and Dustan (1959), Richardson and Wyso (1959), Frohlich and Freis (1959), Leishman *et al.* 1959), Jaquerod and Spühler (1960), Dollery *et al.* (1960), and others. The first preliminary Australian report, including some pharmacological observations, came from Barnett *et al.* (1960). All of these stressed that this drug constituted a definite advance in the management of severe hypertension and underlined the fact that it is free from the parasympathetic blocking effects which had made treatment with hexamethonium, pentolinium, chlorisondamine, mecamylamine, and pempidine often difficult.

Our experiences during the past 12 months have largely confirmed these early impressions. We have found guanethidine a very suitable drug for the long-term treatment of a large proportion of hypertensive patients in whom blood-pressure reduction has been thought advisable. The slow and cumulative effects of this compound have raised some new problems, but on the whole have made long-term treatment and supervision easier than with most other potent hypotensive agents.

Guanethidine is the first of the ganglion-blocking and adrenergic-blocking agents suitable for out-patient stabilization. We have found it preferable to begin with a small dose of guanethidine, such as 12.5 mg. given in one single daily dose, and gradually increase the dose at weekly intervals until an adequate response, as judged by a satisfactory fall in the standing blood-pressure or the appearance of hypotensive symptoms, is obtained. Used in conjunction with saluretic agents, chlorothiazide or hydrochlorothiazide, the effective dose of guanethidine was between 12.5 and 75 mg. a day.

On account of the slow action we do not regard the drug as very suitable for the control of hypertensive crises such as acute left ventricular failure with pulmonary oedema or encephalopathy. Under those circumstances we would prefer to use parenteral pentolinium or, better still, parenteral chlorisondamine, which lower blood-pressure within minutes.

The cumulative effect of guanethidine may lead to the appearance of prolonged hypertensive symptoms even after apparently satisfactory control without change in dosage. We have observed several times that patients discharged from hospital on a daily dose of 50 mg. develop severe giddiness and weakness, especially in the morning hours on resuming normal activities, and are eventually well stabilized on no more than 12.5 mg. We think it important to be particularly cautious in three groups of patients in whom prolonged and excessive lowering of blood-pressure may well be detrimental: (1) those with incipient and frank renal failure; (2) those with a history of recent cardiac infarction or recent cerebrovascular accident; and (3) elderly patients with advanced atheroma. If treatment with guanethidine is begun under those circumstances closest supervision is obviously essential.

Although only a quarter of our patients were completely free from side-effects, these, with few exceptions, were not very troublesome. Apart from hypotensive symptoms, diarrhoea and nasal blockage were the commonest causes of complaint and were alleviated by the passage of time or by simple symptomatic measures.

Our main concern was the appearance or aggravation of depressive symptoms in four patients during guanethidine therapy leading to suicide in one and readmission to a mental hospital in another. Although it is fairly certain that at least three of these patients were of psychopathic personality and that their psychiatric disability may well have been independent of any hypotensive therapy, it is difficult at this early stage in our experience to exonerate guanethidine completely as at least a precipitating or contributing factor. This suspicion is strengthened by a similar observation of Dollery *et al.* (1960), who reported that two of their patients developed severe depressive states with suicidal thoughts during guanethidine treatment. Awareness of this possibility, thus creating a need for continued supervision, may prevent a repetition of the unfortunate consequences of overenthusiastic and indiscriminate reserpine therapy. Other features support this analogy between guanethidine and reserpine: both drugs interfere with the catecholamine metabolism at sympathetic-nerve endings, the clinical use of both is characterized by similar side-effects such as nasal stuffiness, mild diarrhoea, and a tendency to retain water and salt in the body; and now it appears that both may induce or at least aggravate depressive states.

Two favourable aspects of guanethidine remain to be stressed. First, the absence of any significant development of drug tolerance, one of the major disappointments of bretylium tosylate therapy; and, secondly, the absence of any toxic drug effects on liver, kidney, or haemopoietic organs.

Comparison of guanethidine with the specific sympathetic blocker and other anti-adrenergic substance, bretylium tosylate, becomes unavoidable. Although in their main pharmacological action these two drugs appear to be essentially similar, there are certain differences which have an important bearing on their practical use in clinical medicine.

1. Each drug has been shown to have its own peculiar side-effects. Bretylium commonly causes parotid pain and muscle weakness, while guanethidine is more likely to induce diarrhoea and seems to be associated in some patients with the appearance of depressive symptoms.

2. Drug tolerance is a frequent problem with bretylium; with increasing length of observation it has become obvious that many patients require increasing quantities of the drug. This unfortunately necessitates frequent visits to the clinic or the physician's consulting-room, resulting in increased loss of time from work and domestic duties and leading to excessive economic burdens, as well as placing a great strain on the medical staff. So far, tolerance has not been a problem with guanethidine, although minor adjustments in drug dosage may occasionally be necessary.

3. The prolonged action of guanethidine makes it possible not only to administer the drug in a single daily dose but also to estimate its effectiveness with fewer blood-pressure readings. Bretylium has a shorter duration of action and is given in three divided doses a day. It is therefore essential to take several blood-pressure readings at various intervals after administration of the drug to assess its effectiveness.

4. Although neither drug is fully absorbed from the gastro-intestinal system, guanethidine is somewhat superior and gives more constant day-by-day blood-pressure reduction. The incomplete and irregular absorption of bretylium is partly responsible for the unpredictable hypotensive effects, not unlike those seen in the early days of oral hexamethonium treatment.

5. The number of tablets required is less with guanethidine than with bretylium; and this, in our opinion, is a definite advantage. The largest dose of guanethidine prescribed by us was 75 mg. a day—three 25-mg. tablets. With bretylium we have given up to 3,000 mg. a day, or 15 200-mg. tablets, and to many of our patients this has been a definite psychological hardship, quite apart from the bitter taste and large bulk of the tablets.

In summary it is felt that guanethidine is a more suitable drug for routine clinical use.

Summary

Guanethidine sulphate, a new potent oral hypotensive agent, was administered to 28 patients for a period of up to 12 months. This drug selectively blocks adrenergic nerve transmission, leading to sympathetic inhibition with marked postural falls in blood-pressure without any parasympathetic blocking effects such as blurred vision, dryness of mouth, constipation, and bladder atony. Its prolonged action makes it suitable for long-term out-patient treatment provided certain precautions are taken. It is best given in conjunction with saluretic agents such as chlorothiazide or hydrochlorothiazide. Drug tolerance has not been a problem, and side-effects have been slight except for the appearance of depressive symptoms in four patients. Guanethidine has been compared with another adrenergic blocking agent and has been found to be a more suitable drug for routine clinical use.

We are grateful to Dr. V. G. Balmer and Dr. H. H. Knop, of Ciba Company Pty. Ltd., for a generous supply of guanethidine sulphate ("ismelin") and up-to-date information concerning the drug. We thank the members of the nursing staff of the cardiovascular clinic and the clinical research department, Sydney Hospital, for their kind help. This work was undertaken with the aid of a grant from the Post-Graduate Medical Foundation, which we are happy to acknowledge.

REFERENCES

Barnett, A. J., Kincaid-Smith, P., and Simpson, F. O. (1960). *Med. J. Aust.*, **2**, 617.
Bauer, G. E. (1955). Ibid., **2**, 727.
—— (1961). *Jap. Circulat. J.*, **25**, 49.
—— Edwards, A. W. T., Ritchie, F. L., and Whyte, H. M. (1959). *Med. J. Aust.*, **2**, 33.
—— Ritchie, F. L., and Whyte, H. M. (1957). Ibid., **2**, 427.
Boura, A. L. A., Green, A. F., McCoubrey, A., Laurence, D. R., Moulton, R., and Rosenheim, M. L. (1959). *Lancet*, **2**, 17.
Croll, F. J. T., Bauer, G. E., Raftos, J., Goldrick, R. B., and Young, A. A. (1961). *Med. J. Aust.*, **2**, 98.
Dollery, C. T., Emslie-Smith, D., and Milne, M. D. (1960). *Lancet*, **2**, 381.
Frohlich, E. D., and Freis, E. D. (1959). *Med. Ann. D.C.*, **28**, 419.
Jaquerod, R., and Spühler, O. (1960). *Schweiz. med. Wschr.*, **90**, 113.
Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
Leishman, A. W. D., Matthews, H. L., and Smith, A. J. (1959). *Lancet*, **2**, 1044.
Maxwell, R. A., Mull, R. P., and Plummer, A. J. (1959). *Experientia (Basel)*, **15**, 267.
Page, I. H., and Dustan, H. P. (1959). *J. Amer. med. Ass.*, **170**, 1265.
Paton, W. D. M., and Zaimis, E. J. (1948). *Nature (Lond.)*, **162**, 810.
Richardson, D. W., and Wyso, E. M. (1959). *Virginia med. Mon.*, **86**, 377.
Sheppard, H., and Zimmerman, J. (1959). *Pharmacologist*, **1**, 69.

METHOSERPIDINE

A NON-DEPRESSANT ISOMER OF RESERPINE

BY

MARY C. HOLT, M.D., M.R.C.P.
Physician, Royal Eye Hospital, London

In the treatment of moderate hypertension reserpine is often the drug of choice, particularly in the older patient in whom a precipitate fall in blood-pressure, such as can occur during administration of the ganglion-blocking and adrenergic blocking agents, may lead to coronary or cerebral thrombosis. Unfortunately, its usefulness may be limited by side-effects, which can be severe. Platt and Sears (1956), for example, were forced to discontinue treatment because of mental depression in 10 out of 54 cases, and found that over half the patients complained of drowsiness and nasal stuffiness. Palmer (1961) has pointed out that rauwolfia alkaloids may cause mild suppression of mental alertness and diminished intellectual capacity, which can be serious in brain workers. He believes this to be far more common, and therefore more important, than the occasional instances of serious mental depression and of the other well-known side-effects. Animal experiments and early clinical studies have suggested that the synthetic isomer of reserpine, methoserpidine

(" decaserpyl "), is relatively free from these undesirable side-effects while retaining hypotensive potency.

The synthesis of methoserpidine (formerly named 10-methoxydeserpidine) was described by Velluz *et al.* (1958a), and subsequent animal studies with the drug showed that, whatever the dosage used, route of administration, or animal species, there was retention of the hypotensive action of reserpine with loss of the central depressant effect (Velluz *et al.*, 1958b). In rats made hypertensive by implantation of deoxycortone acetate and saline drinks, administration of methoserpidine over a period of a month produced a much more effective hypotensive response than was seen with reserpine (Peterfalvi and Jequier, 1960). In addition, methoserpidine is noticeably less toxic, its LD_{50} being found by Mir and Lewis (1960) to be 82 mg./kg. in mice, whereas that of reserpine is 8 mg./kg. The greater chronic toxicity of reserpine has been demonstrated in animals by Peterfalvi and Jequier (1960). Ten rats were given 1 mg. of methoserpidine per kg. daily for two months and remained in good condition, whereas there was a 50% mortality among a second group receiving reserpine in the same dosage. Mir and Lewis (1960) confirmed the dissociation between hypotensive and central depressant effects using methoserpidine. They observed that, in mice, drowsiness and reduction of motor activity were seen only with the higher doses, and were much less severe than with reserpine or deserpidine. Moreover, loose stools did not occur. Similarly, La Barre (1960) concluded from his experiments that methoserpidine had reduced toxicity and sedative properties without a concomitant reduction of hypotensive action, and also showed less tendency to produce gastric ulceration and vomiting.

Material and Methods

Thirty patients were studied (21 women and 9 men), their ages ranging from 44 to 86 years, with an average of 64 (see Table I). All were ambulant and treated entirely as out-patients. The series included every patient with hypertension referred to the physician's clinic of an eye hospital during an eight-month period in 1960, apart from one case of malignant hypertension treated as an in-patient and those whose rise in blood-pressure was considered insufficient to warrant specific therapy. All patients included in the trial had hypertension of essential type, and there was a high proportion

TABLE I.—*Summary of Findings in* 30 *Patients Treated with Methoserpidine*

Case No.	Age and Sex	Months of Observation	Initial B.P.	Final B.P.	Daily Dosage (mg.)	Response	Side-effects	Comments	Ocular State	
									Before Treatment	After Treatment
1	72 F	6	210/110	170/90	30→10	Good	Nasal stuffiness	Relieved by reduction dosage		
2	67 F	5	190/110	140/75	15	,,				
3	47 M	9	190/105	130/80	40→15	,,			Secondary glaucoma	Eye painless
4	61 F	9	210/115	160/90	20→10	,,			Grade III retinopathy	No change
5	74 M	5	190/110	200/90	15→60	,,			Glaucoma	,,
6	62 M	10	190/100	130/80	15→5	,,	Mild depression	Passed off with continued treatment	C.R.V.T.	Visual "improvement
7	44 F	7	190/120	130/80	30→10	,,			Grade III retinopathy	
8	68 F	7	200/110	160/90	40→15	,,		Pre-existing anxiety depression unaffected	C.R.V.T.	No change
9	56 M	5	200/120	140/80	30→45	,,	Nasal stuffiness	Passed off with continued treatment	Grade III retinopathy	,, ,,
10	70 F	7	170/120	130/85	20→10	,,		Pre-existing anxiety state much improved	Grade II retinopathy	Grade I
11	53 M	7	210/120	170/95	30→20	,,	Drowsiness	Passed off with continued treatment	,, ,,	Normal fundi
12	69 F	5	190/110	180/90	15→60	,,			Post-thrombotic optic atrophy	No change
13	64 M	2	250/130	190/110	30→60	Poor		After 2 months' treatment developed bronchial carcinoma	Grade III retinopathy	,, ,,
14	71 F	7	210/120	190/110	30	,,		Patient defaulted after 7 months		
15	54 F	1	180/100	170/110	10	,,	Headache and nausea	Symptoms recurred after second attempt at treatment. Drug discontinued	C.R.V.T.	,, ,,
16	64 F	6	260/140	150/90	40→30	Good		Pre-existing depression improved		
17	62 F	12	220/140	150/100	30→80	Poor	Fatigue at 80 mg. dosage	,, ,, ,,		
18	65 F	3	220/110	160/90	30	Good		Pre-existing anxiety state improved	Vitreous hæmorrhage	Partial clearing
19	51 M	1	200/125	160/100	15	Poor	Sweating. Fullness in head	Symptom recurred after second attempt at treatment. Drug stopped	Subconjunctival hæmorrhage	Cleared
20	60 F	2	270/125	300/130	60	Fair		Therapy abandoned. Hypertension previously resistant to other hypotensive agents		
21	73 F	6	200/120	180/90	60→40	Good	Drowsiness	Relieved by reduction in dosage	Grade III retinopathy	Grade II
22	78 F	4	210/110	170/110	30→60	Fair			,, ,,	No change
23	68 M	7	180/110	160/90	15→60	Good			Post-thrombotic optic atrophy	,, ,,
24	86 F	4	280/110	195/90	30→60	,,	Slight drowsiness	Passed off without change in dosage	Grade III retinopathy	,, ,,
25	50 M	4	240/140	180/110	30→60	Poor			Specific choroiditis	,, ,,
26	71 F	4	200/130	180/95	15→40	Good	Mild depression	Passed off with continued treatment		
27	68 F	3	240/140	200/105	60	Poor		Defaulted after 3 months' treatment	Myopic degeneration	,, ,,
28	83 F	3	200/110	155/85	15→20	Good		Pre-existing depression improved	Grade II retinopathy	,, ,,
29	60 F	3	200/110	200/105	15→60	Fair	Fatigue at 60 mg. dosage	Changed to guanethidine with satisfactory response	,, ,,	Grade I
30	54 F	3	220/120	140/90	30	Good		Chronic anxiety state improved		

Response: G = Good; P = Poor; F = Failure. C.R.V.T. = Central retinal vein thrombosis.

of elderly and arteriosclerotic subjects. No attempt was made to exclude patients showing signs of mental depression.

It was realized in planning the trial that an appreciable number of the patients would inevitably present with acute retinal vascular lesions, in some cases threatening sight, and under these circumstances the use of a placebo was felt to be unjustifiable.

However, for purposes of comparison data were also collected regarding a consecutive series of 30 patients from the same clinic treated with reserpine during the period immediately preceding the methoserpidine trial. This group had an average age of 61.3 years, and included 19 women and 11 men. The findings with regard to hypotensive action and side-effects are summarized in Tables II and III.

TABLE II.—*Hypotensive Response in Two Groups of 30 Patients Treated with Methoserpidine and Reserpine Respectively*

Response	No. of Cases	Average Fall in Blood-pressure (mm. Hg.)		Average Age in Years
		Systolic	Diastolic	
Methoserpidine (21 Females, 9 Males)				
Good	20	44·5	28·25	64·8
Poor	7	42·9	24·3	60
Failure	3	3·3	0	66
Reserpine (19 Females, 11 Males)				
Good	16	46·2	21	57
Poor	8	25	16	67·5
Failure	6	3·5	9	64

TABLE III.—*Side-effects in Two Groups of 30 Patients Treated with Methoserpidine and Reserpine Respectively. Numbers in Parentheses Show the Instances in which the Drug was Discontinued*

Side-effect	No. of Cases Affected	
	Methoserpidine	Reserpine
Depression	2	4 (4)
Fatigue or drowsiness	5	1
Muzziness	1 (1)	2 (2)
Nasal stuffiness	2	3 (2)
Nausea	1 (1)	0
Diarrhoea	0	1

Before starting treatment the blood-pressure was recorded on at least two separate occasions, the lowest figure obtained being taken as the pretreatment level. Patients attended at intervals of one or two weeks and were seen by me personally throughout the trial, the average period of observation being five and a half months. The examination was carried out at approximately the same time of day on each occasion, the blood-pressure being recorded in the sitting position, without prior sedation or prolonged rest. Information regarding side-effects was specifically sought at every visit.

Treatment was initiated with 15–30 mg. of methoserpidine daily, given in divided doses after the three main meals. Full therapeutic effect was obtained in two weeks in most cases, and the maintenance requirements varied considerably, ranging from 5 to 80 mg. daily. The concurrent use of other hypotensive agents was avoided, but weight reduction was advised where indicated.

Results

Hypotensive Effect.—A fall of diastolic blood-pressure of at least 20 mm. Hg with a final level of less than 100 mm. was accepted as a satisfactory response. Twenty cases, two-thirds of the total, fell into this category (see Table II). In a further seven patients the result was classed as poor, the final diastolic pressure remaining at 100 mm. or above, although in many cases the fall was substantial. In the remaining three subjects methoserpidine in the maximum tolerated dosage failed to affect the blood-pressure level materially. One of these patients had already proved resistant to a wide range of other hypotensive agents. Generally the fall in blood-pressure was progressive, the full effect rarely being achieved in less than four weeks. No evidence of the development of drug tolerance was seen during this trial, but the period of observation was short, and to clarify this point a long-term follow-up is now in progress.

Relief of Symptoms.—There was symptomatic relief in a high proportion of cases, the improvement usually beginning within a few days after starting treatment, and preceding the fall in blood-pressure. Prior to treatment 11 patients showed depressive symptoms, usually associated with anxiety. All but one improved, and five commented spontaneously on an unusual sense of well-being. Of 10 patients complaining of headache and giddiness, eight were completely relieved (often before any effect on the blood-pressure was apparent), and effort angina was much improved in two of the three subjects in whom this symptom was present.

Cardiographic and Ocular State.—During the period of observation only 4 of the 10 patients with cardiographic evidence of hypertrophy ischaemia of the left ventricle showed any improvement, and improvement in retinal grading was found in only 5 of 11 cases showing retinopathy. However, two patients with glaucoma appeared to benefit from the treatment, and in no instance was there deterioration in cardiographic or ocular status.

Side-effects were infrequent and usually mild, necessitating termination of treatment in only two patients, both emotionally unstable individuals with a history of previous drug intolerance. One complained of muzziness in the head and sweating, and the other of headache and nausea, the symptoms in each case returning when the drug was given again after a temporary withdrawal. Mild transient nasal stuffiness which passed off without treatment occurred in three cases (10% of the subjects studied). No complaints of intellectual impairment or loss of mental alertness were received except for five patients (17%) who experienced drowsiness or fatigue. Four of these were taking relatively high doses of methoserpidine, 60 mg. or more daily, and in two the dose had to be cut down, but in the others the symptoms passed off without any change being made. Diarrhoea did not occur, and the fall in blood-pressure was gradual, there being no reports of any episode suggesting postural hypotension. No tendency to increase in weight was apparent, and loss of weight was maintained in those patients who were on reducing diets. As has been mentioned, depressive states present at the onset of treatment were often relieved. Only two patients developed depression during the course of the trial; in both instances the symptom could be adequately explained as a reaction to environmental circumstances, and in neither case was it necessary to stop the drug.

Discussion

The findings in previous clinical trials of methoserpidine are summarized in Table IV. In most the criteria for a satisfactory hypotensive response were similar to those used in the present study, and included

TABLE IV.—*Clinical Trials of Methoserpidine. Summary of Results*

Authors	No. of Cases	Daily Dose (mg.)		Cases Non-malignant Hypertension Showing Satisfactory Hypotensive Response	Side-effects	
		Initial	Maintenance		Depression	Others
Brun and Rondelet (1959)	21	10–30	20–100	76%	Nil	Nasal stuffiness in 2
Mériel *et al.* (1959)	30	10	30–100			Few minor digestive upsets
Mérlen and Gérard (1960)	43	30	20–80	66%	Nil	None
Gros *et al.* (1959)	230	15–30	15–60	58%	Nil	Occasional slight nausea
Tricot *et al.* (1960)	65	30	30–70	65%	Nil	Mild heartburn in 5 (also rhinitis in 2 subsequent to trial)
Read (1961)	15	15	5–15	75%	Nil	Fatigue, 1. Weight gain, 1. Nasal stuffiness, 1
Present series	30	15–30	5–80	66%	2 mild	Sense of unreality, 1. Nausea, 1

a fall of at least 20 mm. in the diastolic pressure. It will be seen that in all the reported trials approximately two-thirds of the cases of non-malignant hypertension showed a satisfactory fall in blood-pressure, and it is of interest that, although only one trial was conducted with placebo control (Tricot *et al.*, 1960), the results here do not differ significantly from the others. In malignant hypertension either the drug has proved to be ineffective (Gros *et al.*, 1959) or a temporary improvement during hospitalization has not been maintained after discharge (Mériel *et al.*, 1959).

Good symptomatic relief has been reported in all the trials of methoserpidine, and Gros *et al.* (1959) note that this often precedes the hypotensive effect, a finding confirmed in the present study.

Most authors have found 30 mg. daily to be a suitable initial dose. Maintenance levels of up to 100 mg. daily have been well tolerated, but both Gros *et al.* (1959) and Tricot *et al.* (1960) feel that 60 mg. daily is probably the maximum effective dose and that patients whose hypertension is not controlled at this level are more satisfactorily treated by the addition of another hypotensive agent.

A study of the published work indicates that the toxic effects of methoserpidine are few, and seldom severe enough to require discontinuance of the treatment, mild nasal stuffiness and slight nausea being those most commonly recorded. No sharp fall in blood-pressure occurs, and, as Gros *et al.* (1959) comment, the drug is therefore particularly suitable for use in elderly arteriosclerotic subjects. More important perhaps is the freedom from mental depressant action, even in the higher dosage levels and after prolonged administration, which has been stressed in all the reported studies. In my own series it is doubtful whether the two mild depressive episodes which occurred were attributable to the action of the drug, and it is of interest that several patients with pre-existing anxiety and depressive symptoms were relieved by methoserpidine therapy. A beneficial action in patients with neurotic symptoms is also noted by Read (1961). The relative freedom from sedative action would seem to indicate a field of usefulness for this drug amongst hypertensive patients in whom mental alertness is of particular importance for the performance of their normal activities.

Comparative figures indicate that methoserpidine is at least as effective as reserpine as a hypertensive agent, while showing a clear advantage in the absence of serious side-effects. A reduction in diastolic blood-pressure of 20 mm. or more was reported in 58–76% of patients in the previous methoserpidine trials (see Table IV), the corresponding figures for reserpine-treated cases ranging from 41.5% in the study by Platt and Sears (1956) to 53% in my own patients (Table II). Depression, which was virtually absent among patients treated with methoserpidine, occurred in 15% of Locket's (1955) series and forced the termination of treatment with reserpine in 18.5% of the cases reported by Platt and Sears (1956), the depression in two subjects being severe enough to lead to suicidal attempts. Nasal congestion, often severe in reserpine-treated cases, has been mild and infrequent among those receiving methoserpidine, and other reserpine side-effects such as gain in weight and diarrhoea seem to be extremely rare, although lethargy or drowsiness is reported in a few patients.

Summary

The report concerns a clinical trial of methoserpidine, a synthetic isomer of reserpine, which has been shown by pharmacological studies to retain the hypotensive action of reserpine without its central depressant effects.

The drug was administered to 30 ambulant patients with hypertension of moderate severity. Two-thirds of the cases showed a good hypotensive result, and serious side-effects were absent. Only two subjects showed depressive reactions, and these were mild and only doubtfully related to the action of the drug. On the other hand, 11 patients with anxiety depression prior to treatment were relieved of their symptoms, and several particularly commented on their sense of well-being.

Although relatively expensive, methoserpidine seems likely to prove a useful hypotensive agent for the patient who is unable to tolerate reserpine owing to side-effects or in whom depression makes the use of this drug unwise. The relative freedom from sedative effect suggests that methoserpidine may also be of value where diminution of mental alertness is particularly undesirable.

I wish to express my thanks to my colleagues at the Royal Eye Hospital who kindly referred cases, and to Dr. A. E. Gremeaux and Mrs. M. Young, of Roussel Laboratories Limited, for their willing assistance and for generous supplies of decaserpyl.

REFERENCES

Brun, F., and Rondelet, J. (1959). *Lyon méd.*, **202**, 843.
Gros, H., Peterfalvi, M., and Jequier, R. (1959). *Algérie méd.*, **63**, 297.
La Barre, J. (1960). *Thérapie*, **15**, 663.
Locket, S. (1955). *Brit. med. J.*, **1**, 809.
Mériel, P., Galinier, F., Suc, J. M., Putois, J., and Bounhoure, J. P. (1959). *Sem. Hôp. Paris*, **35**, 747.
Mérlen, J. F., and Gérard, A. (1960). *Thérapie*, **15**, 488.
Mir, B. J., and Lewis, J. J. (1960). *J. Pharm. Pharmacol.*, **12**, 677.
Palmer, R. S. (1961). *Practitioner*, **186**, 58.
Peterfalvi, M., and Jequier, R. (1960). *Arch. int. Pharmacodyn.*, **124**, 237.
Platt, R., and Sears, H. T. N. (1956). *Lancet*, **1**, 401.
Read, F. H. (1961). *Med. J. Aust.*, **1**, 245.
Tricot, R., Colonna, D., and Alderete, B. (1960). *Presse méd.*, **68**, 905.
Velluz, L., Muller, G., Joly, R., Nominé, G., Mathieu, J., Allais, A., Warnant, J., Valls, J., Bucourt, R., and Jolly, J. (1958a). *Bull. Soc. chim. Fr.*, p. 673.
—— Peterfalvi, M., and Jequier, R. (1958b). *C.R. Acad. Sci. (Paris)*, **247**, 1905.

INCIDENCE OF HYPOKALAEMIA IN SEVERE HYPERTENSION

BY

OLIVER WRONG, B.M., M.R.C.P.*

Assistant to the Medical Unit, University College Hospital, London

The demonstration of an unexplained hypokalaemia in a patient with high blood-pressure is usually thought to be highly suggestive of primary aldosteronism, and has often been the first clue to the correct diagnosis of this disease. In many centres measurement of the serum potassium has become a routine screening test for the detection of cases of this rare and remediable disorder from among the general hypertensive population. This practice presupposes that in hypertension of non-adrenal origin the serum potassium concentration is normal. However, there is some evidence that this supposition is incorrect. De Wesselow and Thomson (1939) pointed out that many hypertensives have a low serum potassium concentration, and Hilden and Krogsgaard (1958) have confirmed this finding; both groups of workers found that hypokalaemia was particularly common in patients with malignant hypertension.

The present survey was undertaken to establish the incidence of hypokalaemia among patients with severe hypertension and, furthermore, to determine what types of hypertension are associated with this abnormality.

Material and Methods

The series consists of patients admitted for the investigation or treatment of hypertension under the care of Professor M. L. Rosenheim over a period of 22 months from January, 1959, and includes all such patients with the following exceptions: those previously admitted for hypertension or already receiving effective treatment; those suffering from diarrhoea, vomiting, congestive heart failure, or severe renal failure (blood urea above 150 mg./100 ml.); and those receiving either steroids or diuretic drugs. Sixty-four patients satisfied these criteria, and all of these had a resting diastolic blood-pressure of 120 mm. Hg or more at the time of admission to hospital. Approximately one-quarter had papilloedema ("malignant" hypertension); in the remainder hypertension was thought to represent a serious hazard to life or was causing severe symptoms.

Patients were thoroughly investigated in the hope of discovering the cause of hypertension. Such study usually included an intravenous pyelogram, and in many cases renal arteriography was performed as well. The plasma potassium was determined by flame photometry, and total carbon dioxide by the method of Van Slyke and Neill (1924). Quoted values of plasma potassium below 3.5 mEq/l. are the mean of at least two determinations on different specimens. The appearances of the optic fundi were classified according to the criteria of Keith *et al.* (1939).

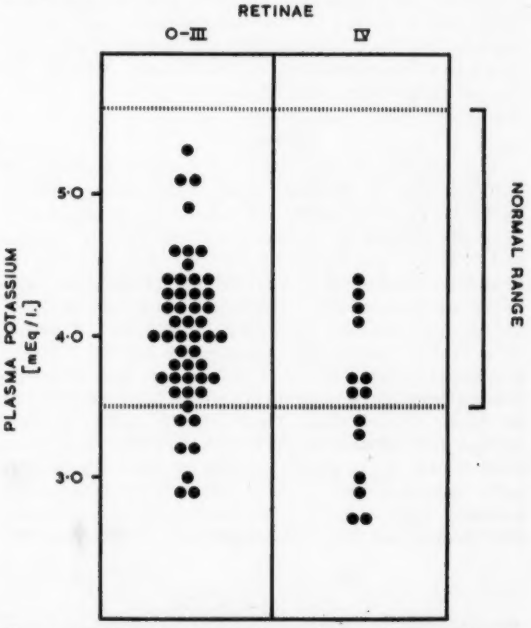
Results

In healthy adults the plasma potassium concentration is less than 3.5 mEq/l. in only 1% of observations (Wootton and King, 1953; Elkinton and Danowski, 1955); Table I and the accompanying Chart show that no fewer than 13 (20%) of the 64 hypertensive patients of this series had a plasma concentration below this figure. When these patients were further classified according to the absence or presence of papilloedema it was found that hypokalaemia was much more common in those with papilloedema (43%). The mean plasma potassium and standard deviation of patients without papilloedema was 4.0 ± 0.5 mEq/l., and of those with papilloedema it was 3.5 ± 0.6 mEq/l.; the difference between the two means is statistically significant ($t=2.9$; $P<0.01$). The incidence of hypokalaemia in each group does not differ significantly from the earlier figures of de Wesselow and Thomson and of Hilden and Krogsgaard (Table I).

TABLE I.—*Incidence of Hypokalaemia in Severe Hypertension*

	Total No. of Hypertensives	Plasma K Below 3·5 mEq/l.	No. Without Papilloedema (fundi O–III)	Plasma K Below 3·5 mEq/l.	No. With Papilloedema (fundi IV)	Plasma K Below 3·5 mEq/l.
Present series	64	13(20%)	50	7(14%)	14	6(43%)
de Wesselow & Thomson (1939)*	35	6(17%)	31	3(10%)	4	3(75%)
Hilden and Krogsgaard (1958)	32	5(16%)	25	1(24%)	7	4(57%)
Total	131	24(18%)	106	11(10%)	25	13(52%)

* One of de Wesselow's patients, in whom hypokalaemia might have been due to vomiting, is omitted.



Plasma potassium in hypertensive patients. The normal range includes 98% of normal observations (Wootton and King, 1953).

Some details of the 13 hypokalaemic patients of this series are given in Table II. The lowest plasma potassium encountered was 2.7 mEq/l. Many of the patients with hypokalaemia also had an alkalosis, and this finding was more frequent in those with malignant hypertension. Investigation revealed possible renal causes of hypertension in 9 (69%) of 13 patients, and five of these had evidence of renal ischaemia on one or both sides. No patient was shown to have an adrenal tumour; in Cases 9, 12, and 13 the adrenals were found to be tumour-free at subsequent necropsy, and in Case 8 the right adrenal appeared normal at the time of right nephrectomy.

*Now at the London Postgraduate Medical School.

These hypokalaemic patients had few symptoms of potassium depletion. A single attack of tetany occurred in Case 8, but no patient had ever suffered from paralysis. The majority complained of nocturia, and some patients had to pass urine as often as eight times a night. Nocturia is a common symptom in primary aldosteronism (Brooks *et al.*, 1957), where it is associated with an inverted diurnal rhythm in the excretion of sodium and water (Lennon *et al.*, 1961): this inverted rhythm also appears to be usual in the syndrome under discussion (Gowenlock *et al.*, to be published). A history of nocturia was found to be of help in predicting whether a hypertensive patient would have hypokalaemia.

In only one hypokalaemic patient (Case 8) of this series was hypertension cured by renal surgery (nephrectomy and excision of phaeochromocytoma compressing renal artery), and in this patient the plasma potassium and total carbon dioxide returned to normal within a few days of operation. Since this study, Cases 2 and 11 have been treated with potent hypotensive drugs for a period of 14 months, and their blood-pressure has been satisfactorily controlled; the plasma potassium concentrations of both were in the low normal range when recently determined.

Discussion

The present demonstration of a high incidence of hypokalaemia in patients with hypertension, and in particular in those with malignant hypertension, confirms the findings of de Wesselow and Thomson (1939) and of Hilden and Krogsgaard (1958). Similar observations have been made by Laragh *et al.* (1960b), but their paper was primarily concerned with the measurement of aldosterone-secretion rates (see below), and it is not clear to what extent their hypertensive patients were an unselected group. The contrary finding, that in hypertension the serum potassium is normal, has been reported by Albert *et al.* (1958). These workers appear to have studied less severely hypertensive subjects than those cited above or the present series, for their 26 patients with "essential" hypertension were all out-patients and included only one case of malignant hypertension. Furthermore, in their discussion and conclusions they made no mention of the fact that their series of hypertensive subjects included three with definite hypokalaemia (serum potassium 3.1, 3.4, and 3.4 mEq/l.); whether one of these was the patient with malignant hypertension is not stated.

The fact which most clearly emerges from the present investigation and the two comparable studies is that a definite hypokalaemia (2.7–3.4 mEq/l.) is present in about 50% of patients with malignant hypertension (Table I). This hypokalaemia is often accompanied by a mild alkalosis. The more common causes of potassium depletion, such as increased alimentary loss or the diuresis produced by drugs of the chlorothiazide type, were excluded by the initial selection of the present series. Metabolic observations on some of these and similar patients (Gowenlock *et al.*, to be published) have shown that their hypokalaemia is accompanied by impaired renal conservation of potassium, between 40 and 70 mEq of this electrolyte being lost in the urine daily. Such renal wastage of potassium could theoretically result either from primary renal disease or from an excessive adrenal secretion of aldosterone or some other mineralocorticoid. Potassium-losing renal disease seems unlikely here, for it is almost invariably accompanied by an acidosis, not an alkalosis, and usually by other signs of renal tubular damage, such as amino-aciduria, glycosuria, or nephrocalcinosis, none of which were demonstrated in the present cases. But hyperaldosteronism when it causes potassium depletion also frequently results in an alkalosis. Measurements of urinary aldosterone were made in only two of our patients (Cases 8 and 11), and one of these (Case 8) was found to be excreting increased amounts (Gowenlock and Wrong, 1961).

Evidence that hypertension is commonly accompanied by hyperaldosteronism has appeared in the recent medical literature. Genest *et al.* (1960) have found that aldosterone excretion is increased in a large proportion of hypertensive patients, particularly so in those with malignant and renal hypertension. Garst *et al.* (1960) excluded from their series all patients with malignant hypertension or obvious renal disease, but nevertheless found that in a large proportion of patients with essential hypertension the excretion of aldosterone was raised.

Details of Hypokalaemic Hypertensives

Case No.	Sex and Age	Fundi	Plasma K mEq/l.	Plasma Total CO_2, mM/l.	Cause of Hypertension	Follow-up
				Without Papilloedema		
1	F 14	I	2·9	30·6	Renal (chronic pyelonephritis, double left ureter, urethral bar, and bilateral vesico-ureteric reflux)	—
2	M 26	0	3·4	29·6	?Essential. Idiopathic Hypoparathyroidism.	Plasma K 4 mEq/l. after 14 months' hypotensive therapy
3	F 32	I	3·2	27·6	Renal (stricture right renal artery)	Anxiety neurosis; unable to attend
4	M 45	II	3·2	27·7	?Essential (normal pyelogram, no family history)	—
5	M 46	II	3·0	32·8	?Essential. ?Renal (renal calculus 2 years ago, normal pyelogram, no family history)	—
6	M 47	II	2·9	31·4	Renal (recurrent attacks of pyelonephritis; pyelogram shows clubbed calices)	—
7	M 67	I	3·4	25·4	?Essential (no family history, normal pyelogram)	—
				With Papilloedema		
8	F 25	IV	2·7	32·5	Renal and adrenal medullary (phaeochromocytoma compressing right renal artery)	Normotensive 1 year after operation, plasma K 3·9 mEq/l. Right adrenal normal at operation
9	F 26	IV	3·3	31·2	Renal (aortic aneurysm involving both renal arteries)	Died after aortic resection. Adrenals infarcted as result of surgery, but no tumour
10	M 45	IV	2·9	28·8	Essential (strong family history)	Died in uraemia 6 weeks later; no necropsy
11	M 47	IV	3·0	33·3	Renal (multiple strictures on renal arteries)	K 3·9 mEq/l. after 14 months' hypotensive therapy
12	M 52	IV	2·7	28·7	Renal (chronic glomerulonephritis)	Died of hepatoma. Normal adrenals at necropsy
13	M 53	IV	3·4	27·3	Renal	Died in uraemia 4 months later; necropsy showed normal adrenals and thrombosis of right inferior renal artery

Laragh *et al.* (1960b) have measured secretion rates in a large number of patients with hypertension of various types. In 14 out of 15 patients with malignant hypertension the rate of secretion was greatly increased, lying between 600 and 2,000 μg./24 hours (normal 150–330 μg.). Five patients with primary aldosteronism secreted slightly less aldosterone (510–1,690 μg./24 hours), although the figures of the two groups overlapped. Patients with hypertension and renal or retinal complications other than papilloedema (grade III retinopathy) often had raised secretion rates, but the secretion rates of patients with uncomplicated essential hypertension were normal. Half the patients with malignant hypertension had their adrenal glands examined at subsequent operation or necropsy; no adrenal tumours were found, but bilateral cortical hyperplasia was present in several cases. This work constitutes impressive evidence that hyperaldosteronism is usual in malignant hypertension and common in hypertension of less severe degree. The rates of secretion are as high as those encountered in primary aldosteronism and might be expected to cause a similar hypokalaemia. Laragh *et al.* (1960b) remarked on the frequent finding of a hypokalaemic alkalosis in their patients; 6 out of 15 cases with papilloedema had a serum potassium below 3.5 mEq/l., and three cases had a plasma total carbon dioxide above 31 mM/l. In this respect Laragh's observations tally closely with mine.

From the observations cited above there can be little doubt that the hypokalaemia commonly present in severe hypertension is due to hyperaldosteronism. However, this condition is not primary aldosteronism. The present series and numerous earlier individual case reports (Wrong, 1957; Dollery *et al.*, 1959; Hoet and Molineaux, 1960; Laidlaw *et al.*, 1960; Gowenlock and Wrong, 1961) show that many such patients are discovered at investigation to have renal causes of hypertension—usually renal ischaemia. In such cases appropriate renal surgery alone has often resulted in cure both of hypertension and of the signs of hyperaldosteronism, which suggests that the adrenal hyperfunction is in some way the result of renal disease. Laragh *et al.* (1960a) have found that intravenous injection of angiotensin into normal subjects causes a marked increase in aldosterone secretion, and it may therefore be through the mediation of renin that renal disease brings about a state of hyperaldosteronism. Not all the hypokalaemia patients of this series were shown to have primary renal disease; but the above thesis is not thereby invalidated, for severe hypertension of any origin may damage the kidney and lead to focal areas of ischaemia. Alternatively, it may be that severe hypertension itself stimulates aldosterone secretion, but there is no experimental support for this hypothesis.

Conn (1960) has suggested that the diagnosis of primary aldosteronism would be made much more often if the plasma potassium were determined as a routine in cases of hypertension. While this conjecture is almost certainly true, the present study does suggest that the majority of untreated hypertensives who are found to have hypokalaemia are not, in fact, suffering from primary aldosteronism.

Summary

Of 64 patients with severe hypertension, 13 (20%) had a definite hypokalaemia (plasma potassium 2.7–3.4 mEq/l.), often accompanied by an alkalosis. The incidence of hypokalaemia was greatest in those with papilloedema (43%). Possible renal causes of hypertension were discovered in two-thirds of those with hypokalaemia.

The hypokalaemia of severe hypertension seems to be due to hyperaldosteronism, which is caused by renal ischaemia, the hypertension itself, or some closely related phenomenon. The term "primary" aldosteronism is not applicable to this syndrome.

REFERENCES

Albert, D. G., Morita, Y., and Iseri, L. T. (1958). *Circulation*, **17**, 761.
Brooks, R. V., McSwiney, R. R., Prunty, F. T. G., and Wood, F. J. Y. (1957). *Amer. J. Med.*, **23**, 391.
Conn, J. W. (1960). *J. Amer. med. Ass.*, **172**, 1650.
de Wesselow, O. L. V. S., and Thomson, W. A. R. (1939). *Quart. J. Med.*, **8**, 361.
Dollery, C. T., Shackman, R., and Shillingford, J. (1959). *Brit. med. J.*, **2**, 1367.
Elkinton, J. R., and Danowski, T. S. (1955). *The Body Fluids*. London.
Garst, J. B., Shumway, N. P., Schwartz, H., and Farrell, G. L. (1960). *J. clin. Endocr.*, **20**, 1351.
Genest, J., Koiw, E., Nowaczynski, W., and Sandor, T. (1960). *Acta endocr. (Kbh.)*, **35**, 413.
Gowenlock, A. H., de Graeff, J., Stanbury, S. W., and Wrong, O. To be published.
—— and Wrong, O. (1961). In press.
Hilden, T., and Krogsgaard, A. R. (1958). *Amer. J. med. Sci.*, **236**, 487.
Hoet, J. J., and Molineaux, L. (1960). *Acta endocr. (Kbh.)*, **33**, 375.
Keith, N. M., Wagener, H. P., and Barker, N. W. (1939). *Amer. J. med. Sci.*, **197**, 332.
Laidlaw, J. C., Yendt, E. R., and Gornall, A. G. (1960). *Metabolism*, **9**, 612.
Laragh, J. H., Angers, M., Kelly, W. G., and Lieberman, S. (1960a). *J. Amer. med. Ass.*, **174**, 234.
—— Ulick, S., Januszewicz, V., Deming, Q. B., Kelly, W. G., and Lieberman, S. (1960b). *J. clin. Invest.*, **39**, 1091.
Lennon, E. J., Ruetz, P. P., and Engstrom, W. W. (1961). *Amer. J. Med.*, **30**, 475.
Van Slyke, D. D., and Neill, J. M. (1924). *J. biol. Chem.*, **61**, 523.
Wootton, I. D. P., and King, E. J. (1953). *Lancet*, **1**, 470.
Wrong, O. (1957). *Quart. J. Med.*, **26**, 586.

INTRATHECAL TUBERCULIN IN DISSEMINATED SCLEROSIS

A CONTROLLED TRIAL

BY

R. E. KELLY, M.D., F.R.C.P.

AND

E. H. JELLINEK, D.M., M.R.C.P.

St. Thomas's Hospital and Maida Vale Hospital, London

When Smith *et al.* (1957) published a hint of prolonged remissions in disseminated sclerosis after an experimental study of cerebrospinal fluid (C.S.F.) changes with intrathecal tuberculin injections (purified protein derivative—P.P.D.) we felt obliged to test this. For reasons which must be obvious (see also *British Medical Journal*, 1958) we set about a controlled trial.

In order to obtain early results we deliberately selected 20 patients with undoubted disseminated sclerosis in whom we thought further demyelination probable—that is, we chose patients with at least three episodes occurring at a rate of more than one a year, or with evidence of unremitting progression over six months. They all had some signs of damage to the central nervous system, but were still useful members of society or of their household, with measurable faculties to lose. They were unaffected by pulmonary tuberculosis or general medical diseases or psychiatric disorders.

If after due explanation of the expected risks they agreed to this experimental course of treatment they were admitted under the care of one of us (R. E. K.) to Maida Vale Hospital or St. Thomas's Hospital. By kind permission of the other physicians at Maida Vale we selected from their much larger number of cases 20 controls who were matched as closely as possible for age, sex, length and activity of disease, and actual incapacity (see Table I).* Two of the trial cases (Nos. 8 and 14) and one of the control cases (No. 4) had an affected parent or sibling. Table II summarizes the main data of the two groups.

TABLE I.—*Clinical Histories up to Date of Trial*

No.	Trial Cases	Control Cases
1	Male shipping agent aged 37 in 1958. 4 episodes in 3 years. Good recoveries. Working.	Male lorry driver aged 42 in 1958. 4 episodes in 3 years. Good recoveries. Working.
2	Male photographic grader aged 30 in 1958. 4 years of progressive disability. Moderately disabled but working.	Male grocer aged 29 in 1958. Progressive disorder for 4 years. Part-time work. Walking limited to 50 yards.
3	Housewife aged 42 in 1958. 9 episodes in last 8 years. Fair recoveries. Some limitation of normal activities.	Male compositor aged 35 in 1958. 7 episodes in 7 years. Good recoveries. Full-time work.
4	Male insurance clerk aged 32 in 1958. 15 episodes in 9 years. Fair recoveries. Limited homework.	Housewife aged 32 in 1958. Brother died of disseminated sclerosis. 14 episodes in 9 years. Fair recoveries. Limited housework.
5	Clerk and housewife aged 35 in 1958. 8 episodes in 6 years. Fair recoveries. Full housework, but retired from clerical job.	Housewife aged 43 in 1958. 9 episodes in 9 years. Fair recoveries. Limited housework.
6	Housewife aged 43 in 1958. 3 episodes in 2 years. Good recoveries. Normal activity.	Housewife aged 43 in 1958. 4 episodes in 2 years. Good recoveries. Full domestic activity.
7	Schoolmaster aged 37 in 1958. 9 episodes in 8 years. Fair recoveries. Wheel-chair, but still doing literary work.	Male estimator in aircraft factory aged 43 in 1958. 6 episodes in 7 years. Fair recoveries. Moderately disabled, but still working.
8	Housewife aged 46 in 1958. Father died of disseminated sclerosis. 8 episodes with good recoveries 1940–52. Progressive disorder for last 6 years. Wheel-chair, but a fair amount of housework.	Housewife aged 48 in 1958. Episode with remission 15 years ago. Progressive disorder for last 4 years. Limited housework.
9	Housewife and secretary aged 35 in 1959. 6 episodes in 3 years. Good remissions. Full housework, but some limitation of secretarial work.	Housewife aged 25 in 1959. 10 episodes in 5 years. Good remissions. Slight limitation to housework.
10	Male electrician's mate aged 26 in 1959. 6 episodes in 2 years. Good recoveries. Full work.	Male instrument mechanic aged 23 in 1959. 6 episodes in 2 years. Good recoveries. Full-time work.
11	Housewife aged 38 in 1959. 4 episodes in 3 years. Poor recoveries. Limited housework. Wheel-chair.	Housewife aged 44 in 1959. 4 episodes in 3 years. Poor recoveries. Limited housework. Wheel-chair.
12	Businessman aged 44 in 1959. 5 episodes in 4 years. Fairly good recoveries. Full activities and only slightly disabled by giddiness.	Maintenance foreman aged 43 in 1959. 4 episodes in 2 years. Good recoveries. Some residual giddiness, but full activities.
13	Housewife aged 53 in 1959. First episode 36 years ago with complete recovery. During last 7 years 4 further episodes with incomplete recovery and progressive spasticity for last 3 years. Limited housework.	Housewife aged 64 in 1954. 3 episodes in 34 years with progressive paraplegia in last 9 years. Limited housework.
14	Housewife aged 45 in 1959. Mother afflicted with disseminated sclerosis. Remitting episode 23 years ago, but progressive illness for last 13 years. Limited housework.	Housewife aged 41 in 1959. 6 episodes in 15 years with slow progression over the last 11 years. Limited housework.
15	Female clerk aged 22 in 1959. 4 episodes in 3 years. Very good remissions. Normal work.	Housewife and typist aged 26 in 1959. 4 episodes in 3 years. Good recoveries. Well and working. Six months pregnant at time of trial.
16	Housewife aged 52 in 1959. More than 13 episodes in 13 years. Poor remissions during last 3 years. Limited housework.	Housewife aged 34 in 1959. 21 episodes in 12 years. Fair recoveries. Limited housework.
17	Female teacher aged 51 in 1959. Progressive disorder for last 6 years. Full housework only.	Female secretary aged 36 in 1959. Progressive paraplegia for 7 years. Motor wheel-chair and limited clerical work.
18	Milk roundsman aged 51 in 1959. 5 episodes in 4 years. Poor recoveries. Able to work as switchboard operator.	Male garage proprietor aged 50 in 1959. 7 episodes in 7 years. Poor recoveries. Still doing car repairs.
19	Retired police officer aged 43 in 1959. 6 episodes in 5 years. Fair recoveries.	Male local government officer aged 40 in 1959. 6 episodes in 6 years. Fair recoveries. Still working.
20	Male fishmonger aged 49 in 1959. 10 episodes in 15 years. Poor recoveries. Light manual work.	Housewife aged 56 in 1959. 6 episodes in 15 years. Poor recoveries. Limited housework.

*Full clinical histories may be obtained from the authors.

TABLE II.—*Summary of Clinical Features of the Two Groups*

	Trial Group	Control Group
Average age	40½	40
Males	9	8
Females	11	12
Relapsing-remitting course	11	11
Relapses with poor or no remissions	5	5
Relapsing-remitting followed by progressive course	2	2
Progressive course	2	2
Patient-years of disease	174	162
Episodes of demyelination	121	123

Methods

Mantoux tests were done: in the four Mantoux-negative trial cases the reactions were converted to positive by B.C.G. inoculation. Two of the control cases were also inoculated with B.C.G., but otherwise the control cases were treated only by the palliative measures of current neurological practice, and remained under the care of their physicians. The trial cases were assessed clinically, psychometrically, and by the physiotherapists, and were given a course of physiotherapy on admission, if indicated, before the actual treatment.

P.P.D. (Ministry of Agriculture and Fisheries) was injected by lumbar puncture; 0.375 μg. (0.5 ml.) was given at first in all 20 cases. If the C.S.F. protein rose to over 300 mg./100 ml. in the next week or if the clinical reaction was severe no more was injected (11 cases). Nine patients had a second injection of 0.375 to 1.5 μg., and one of these had a third injection of 0.75 μg.

Apart from careful clinical observations serial studies were made of the C.S.F., usually on the first and fifth days after the P.P.D., and then weekly until the reaction was clearly subsiding. C.S.F. and plasma protein changes were also studied electrophoretically and serial E.E.G. recordings were made in most cases.

After discharge all the trial cases were seen by us personally at intervals of three months or less. Nineteen of the control cases were also seen by us during and at the end of the follow-up period, but a little less often as they remained under the care of their own physicians. We are obliged to the family doctor for the follow-up of control case No. 17, who moved to the North of England. Psychometric tests were repeated about the sixth and twelfth months.

Results

Ten cases were treated at St. Thomas's Hospital and 10 at Maida Vale Hospital between August, 1958, and September, 1959.

Immediate Clinical Reaction.—A febrile reaction with signs of meningeal irritation occurred after 19 out of the total of 30 intrathecal injections. This subsided in one to three days and never gave cause for anxiety. Nine patients experienced exacerbation of their symptoms and signs, and six required catheterization of the bladder. Eight recovered to their pretreatment state, usually within a few days, but Case 2 remained more spastic. The severity of the clinical reaction was not mirrored in the C.S.F. changes.

Clinical Progress Until Discharge

Fourteen patients progressed uneventfully. Bladder infections occurred in six cases (Nos. 4, 5, 9, 14, 16, and 20)—in four of these in association with neurological setbacks. Episodes of further plaques of

demyelination occurred in five cases after the immediate clinical or meningeal reaction had subsided.

Case 5 became much more ataxic with increasing weakness of the lower limbs on the twelfth day after treatment, and this had not resolved at the time of discharge. Case 14 developed increasing weakness of the upper limbs between the eleventh and the twentieth day after treatment. She also developed retention of urine and had not recovered her pretreatment state at the time of discharge three months later, although improved. Case 19 developed a complete left foot-drop 10 days after the first injection of tuberculin. This had resolved completely at the time of discharge.

In two other cases the new episodes were alarming.

Case 9 was given 0.375 μg. of P.P.D. without much reaction. On the eighth day she developed numbness of the second division of the trigeminal nerve on the right and the left side, apparently a reactivation of an old plaque 11 months previously. She was given a second injection of 0.75 μg. 12 days after the first. The immediate meningeal reaction was not severe. On the third day after the second injection she developed motor and sensory signs in her left lower limb; these increased gradually up to the 20th day, by which time she had loss of anal sensation, complained of bladder symptoms, and was in a state of agitated depression. On the 24th day she also developed motor and sensory symptoms in the right leg and was frankly suicidal; a course of E.C.T. was started. On the 30th day she presented the picture of an ascending myelitis with intercostal paralysis and a respiration rate of 28. On the 34th day the paraplegia was complete, and she had a fourth plaque with right-sided facial paralysis and dysarthria. On the 41st day there was a fifth plaque with left-sided deafness and a bulbar palsy. Treatment with prednisone, 60 mg. daily, was started. She had a fourth E.C.T. for her persistent depression. On the 46th day the bulbar palsy was improving but she had a sixth plaque in the form of an acute attack of left retrobulbar neuritis, having been on a large dose of prednisone for the previous five days. Thereafter she improved slowly: visual acuity had returned to normal three months after the tuberculin and she was discharged home, still incontinent and paraplegic, four months later.

Case 20 was given 0.375 μg. of P.P.D. and had a brisk meningeal reaction lasting three days with transient retention of urine. Thereafter he returned to his pretreatment state until the 19th day. On this day he lost control of his bladder and the following day he had signs of a spinothalamic plaque in the dorsal region. By the 23rd day he required catheterization and had signs of a complete cord transection in the mid-dorsal region. On the same day he developed increasing weakness of his left upper limb and visual acuity in the right eye diminished from J1 to J8. Two months later there was some recovery of spinothalamic sensation in the lower limbs, but he still had an indwelling catheter and a chronic urinary infection. He was transferred to a hospital for chronic cases four months later, still completely paraplegic.

The trial cases were discharged between 4 and 18 weeks after the tuberculin injections (mean 7½ weeks). At the time of discharge 13 of the patients were improved or unchanged and seven were worse than on admission.

Serial E.E.G.s were done before and during the reactions and at the time of discharge in all the Maida Vale cases, and showed no significant change.

C.S.F. Changes

The C.S.F. protein increased with the reactions: in 10 patients the peak occurred on the first day, in the rest about the fifth day except in Case 5, where it was delayed till the twelfth day, and in Case 20, where a second higher peak was observed on the fiftieth day (Table III). A second or third injection, even of the same amount, produced a higher rise of protein on all but one occasion (Case 10).

The cellular reaction was variable; it was maximal on the first day on nine occasions but delayed until the third to eighth day in 14 reactions. Three patients with a delayed cellular response to the first P.P.D. injection gave a first-day response to a second injection.

TABLE III—*Predominant C.S.F. Changes After Intrathecal P.P.D.*

Case No.	Dose of P.P.D. (μg.)	1st Day			Maximum 3–8 Days	
		Total Cells	% Polymorphs	Protein	Total Cells	Protein
1	0·375	1	0	83	24	52
	1·5	38	15	490	320	225
2	0·375	21	26	98	150	480
3	0·375	249	87	80	190	232
	1·125	400	14	380	103*†	194
4	0·375	65	0	210	239	400
5	0·375	63	0	105	255	220†
6	0·375	6	0	65	217	90
	1·125	2,025	80	240	178	120
7	0·375	29	0	200	260	570
8	0·375	9	60	65	113	320
9	0·375	15	0	60	181	140
	0·75	Not counted		185	99	220
10	0·375	30	0	80	218	160
	0·75	Not counted		70	—	95
	0·75	31	?	400	—	110
11	0·375	3,300	85	220	440	295
12	0·375	247	0	190	—	210
13	0·375	282	76	60	131	35
	0·375	705	38	90	240	57
14	0·375	1,343	95	114	93	77
15	0·375	2	?	25	61	75
	0·75	543	?	300	91	80
16	0·375	30	?	50	65	155
	0·75	>1,000	90	475	203	165
17	0·375	192	?	340	578	325
18	0·375	—	—	—	358	325
19	0·375	—	—	—	195	110
	0·75	565	?	850	290	475
20	0·375	176	68	116	286	600‡

* 5th day: 64% polymorphs. †12th day: protein 326 mg./100 ml. ‡ 50th day: protein 650 mg./100 ml.

The maximum cell count in each case ranged between 100 and 1,000 in 16 cases, and over 1,000 in four cases (No. 6, 2,025; No. 11, 3,300; No. 14, 1,343; No. 16, >1,000). The cell count had usually subsided to fewer than 100 after a month.

The cellular reaction of the first day was mainly polymorphic in six patients. In another case polymorphs predominated on the fifth day (No. 3). Otherwise the first-day reactions were lymphocytic, as were all later cell-counts in all cases.

Follow-up Period

The periods of observation in the two groups from the date of the first P.P.D. injection ranged from 16 to 29 months (mean 22½ months). Table IV gives the events and end-results in the two groups. In summary, these were as shown in Table V at the end of the follow-up period.

Serial psychometric tests showed evidence of deterioration in 9 out of 16 trial cases during the year after the P.P.D.

Discussion

The results indicate quite clearly that the trial group did not benefit from P.P.D., whether one assesses the results from the point of eventual degree of disability or from the number of new episodes. By the first criterion there is probably no significant difference between the two groups.

The number of new episodes was indeed much higher in the treated group (52:31), but this score is inevitably

TABLE IV.—*Clinical Progress of the Two Groups During Follow-up Period*

		Trial Group					Control Group				
	Worse on Discharge	Better or Unchanged	Slightly Worse	Much Worse	Steady Deterioration	New Episodes	Better or Unchanged	Slightly Worse	Much Worse	Steady Deterioration	New Episodes
1		X				1			X		4
2	X			X	X				(X)	X	
3				X		10		X			5
4			X			2		X			2
5	X			X		2	X				
6			X			4			X		3
7	X			(X)	X	3			X		5
8				X	X	3			X	X	
9	X			X		7		X			3
10				X		7	X				
11				X		1			X	X	1
12			X			3		X			1
13				X	X	1		X			1
14	X			X		1		X			1
15			X			2			X		1
16	X			X	X				X		3
17			X				X				
18			X			1			X		1
19		X				1	X				
20	X			(X)	X	3	X				

(X) Died.

TABLE V.—*Comparison of Follow-up Results*

	Trial Cases	Control Cases
Better or unchanged	2	5
Slightly worse	6	6
Much worse (including deaths)	12	9
Deaths	2	1
Continuous deterioration	6	3
New episodes	52	31
No sign of activity of the disease	1	3

directly related to the closeness of medical supervision, and if the 12 episodes observed in the trial group while in hospital after the P.P.D. treatment are subtracted the numbers are more comparable in the two groups. However, the same 12 episodes so soon after the P.P.D. led us to stop the trial in September, 1959.

No significant difference in the clinical progress was observed in two subgroups: (1) *B.C.G. cases* (Nos. 13, 14, 15, and 19 in the trial group, and Nos. 11 and 14 in the control group). (2) Cases with a maximal *C.S.F. protein of more than 500 mg./100 ml.* (Cases 7, 19, and 20), of whom two had died and one was unchanged at the end of the follow-up period.

We were struck by the great variability in the individual C.S.F. reactions in our cases. This seemed to differ from two previous studies. Smith *et al.* (1957), who tended to use larger doses of P.P.D., emphasized a single pattern of response with relatively high protein levels and apparent absence of an early polymorphonuclear reaction. Marshall and O'Grady (1959) described two patterns of response of either a slow rise in protein and cells or of an early peak followed by a later and smaller rise in protein and cells; these patterns were also observed in motor neurone disease, Parkinsonism, and Huntington's chorea.

The significance of the changes in the protein fractions on electrophoresis of the serum and C.S.F. has been discussed elsewhere (Gavrilescu *et al.*, 1961).

Finally, we can unfortunately claim success only for our choice of cases with measurable activity of their disease; our series must not be taken as representative of disseminated sclerosis; as seen generally, this is a much more benign disorder.

Summary and Conclusions

A trial of intrathecal tuberculin (P.P.D.) was made on 20 patients with disseminated sclerosis in whom the disease seemed active and in whom new episodes of demyelination or deterioration were anticipated.

On comparing their fate with a group of 20 carefully matched control cases we conclude that intrathecal tuberculin in disseminated sclerosis is a form of treatment which confers no benefit on the patient, despite the unpleasantness of the reaction and the length of the stay in hospital. Indeed, we are not satisfied that it may not lead to reactivation of the condition during the month after the treatment.

We hope that trials like ours and the similar results of Miller *et al.* (1961) will prevent the use of P.P.D. as a placebo in a condition where there is great pressure for some active form of treatment. Other untested and potentially harmful methods such as intravenous "pyrifer," or arsenic and bismuth, should similarly be abandoned for truly harmless placebos.

We thank the patients who agreed to participate in this trial and the other members of the staff of Maida Vale Hospital who allowed us to follow the progress of the control cases. We are obliged to Dr. Honor Smith for her kind advice on the technique of the P.P.D. course during the planning of this trial: to Miss Marjorie Durward for the psychometric tests; to Dr. H. Townsend for analysis of the many E.E.G. tracings; and to Dr. M. H. Russell for his help in the follow-up of control case No. 17.

REFERENCES

Brit. med. J., 1958, **2**, 1025.
Gavrilescu, K., Jellinek, E. H., and McMenemey, W. H. (1961). *Wld Neurol.* In press.
Marshall, J., and O'Grady, F. (1959). *J. Neurol. Neurosurg. Psychiat.*, **22**, 277.
Miller, H., Ridley, A., Newell, D. J., and Schapira, K. (1961). Ibid. In press.
Smith, H. V., Espir, M. L. E., Whitty, C. W. M., and Russell W. R. (1957). Ibid., **20**, 1.

FAECAL EXCRETION OF ADENOVIRUS IN A CLOSED COMMUNITY

BY

P. S. GARDNER,* M.D., Dip.Bact.

A. E. WRIGHT, M.D., D.P.H., Dip.Bact.

AND

J. H. HALE, O.B.E., M.D., M.R.C.P.

Regional Public Health Laboratory, General Hospital, Newcastle upon Tyne

The adenoviruses are a large group of viruses possessing a common soluble antigen but divisible into no fewer than 23 serological types, of which 18 are of human and five are of simian origin. Since the observation of a spontaneous degenerating agent in human tonsils growing in tissue culture (Rowe *et al.*, 1953), many family and institutional outbreaks of adenovirus infections have been described among civilians (Munro-Ashman *et al.*, 1958). Serological evidence suggests that infection is widespread and probably occurs in children (Huebner *et al.*, 1954), although the exact role of these agents in causing clinical symptoms is not yet clear. Some types, such as 3, 4, and 7, are associated with acute respiratory disease (Berge *et al.*, 1955), type 8 (Jawetz *et al.*, 1955, 1956) is associated with epidemic keratoconjunctivitis. Others, such as 1 and 2, are more often found in human adenoids and tonsils removed at operation. Maternal antibodies to many of these agents are

*Now at the Joint Department of Bacteriology, Royal Victoria Infirmary, and the Medical School, King's College, Newcastle upon Tyne.

found in babies (Morrison *et al.*, 1957); these disappear by 6 months of age and reappear when stimulated to do so by natural infection. These antibodies are not confined to the so-called epidemic strains but may be antibodies to any members of the group. Thus it appears that antibodies are produced against some viruses which cause no clinical signs of infection.

This communication presents the results of a year's study of the excretion of adenoviruses in the stools of children living in a residential nursery, together with an account of the general health of the community throughout the period.

Plan of Investigation

The home was situated in a large country-house which was controlled by a matron and a number of staff, some of whom were qualified nurses, and others who were in training. The domestic staff were recruited locally and lived at home, in contrast to the nursing staff, who were resident. The children were admitted usually to convalesce after some illness or because of domestic difficulties; some children remained for only a few weeks, though the stay was more often measured in months. The children, about 25 in number, lived in two main groups. The first, under 1 year of age, lived in their own nursery; the second, aged from 1 to 6 years, mixed with greater freedom among themselves. There was little contact between these groups, although the attempt to keep them separate usually failed owing to staff shortages at nights and at holiday periods.

Faecal specimens from staff and children were examined at fortnightly intervals for viruses. Ten per cent. suspensions of faeces in distilled water were centrifuged at 10,000 *g* for 30 minutes, and 0.2 ml. of the supernatant was used for inoculating HeLa-cell cultures. Monkey-kidney and amnion-cell cultures were also used when available. Any agents isolated were identified by neutralization with specific antisera.

No attempt was made to examine sera for antibody to viruses as it was thought that periodic bleeding might lead to a loss of co-operation between the children and staff, and, in any case, the primary interest was the spread of viruses in the community. Blood for serology was, however, obtained when a child became ill.

The home was visited at regular intervals in order to compile records of illnesses and to correlate these so far as possible with any virus excretion.

Results

Many types of adenovirus were found to be excreted by the occupants of the home but no seasonal variation was noted, and with the exception of one incident none were related to clinical illness.

Adenovirus types 1, 2, 3, 4, 5, 6, and 7 were all encountered, but type 5 was isolated with far greater frequency (Table I).

TABLE I.—*Total Adenovirus Excretion in the Nursery*

Adenovirus	5	1	6	7	4	2	3
No. of isolations	88	17	9	5	3	2	1

Table II shows the incidence of adenovirus excretion in the babies, the toddlers, and the adults; it can be seen that excretors are more frequent in the young.

Duration of Excretion.—Five children excreted adenovirus type 5 for prolonged periods (three to six months); in fact, one child aged 1 year had excreted this virus in her faeces for nine months when this investigation ceased, so it was conceivable that the period of excretion was much longer. Four of the five children were 1 year of age or under and the fifth was 4 years old. During the period of type 5 excretion one child excreted type 4 and another type 6.

TABLE II.—*Age Incidence of Adenovirus Infection*

Age	No.	Infection with One Type Only During the Investigation	Infection with Two or More Types During the Investigation
<1 year	34	20	7
1–6 years	34	13	5
Adults	21	6	2

Correlation of Virus Excretion with Clinical Disease.—With one curious exception adenovirus appeared to circulate in the community without being associated with or giving rise to respiratory illness, although accepted pathogenic adenovirus types 4 and 7 were isolated on different occasions. In December four children became ill with an infection of the upper respiratory tract which subsequently became an acute bronchiolitis severe enough to necessitate their admission to Newcastle General Hospital. All four children were taken ill within a few days, and the only laboratory finding was the faecal excretion of adenovirus type 5 after the beginning of the illness. In three cases this excretion ceased very shortly after the illness, while the fourth child continued excretion for a further eight weeks. Serological investigations and throat swabs were negative, a not uncommon finding in this condition (Gardiner *et al.*, 1960b).

Discussion

Several features became apparent during this investigation. We were rather surprised by the ease with which the adenovirus could be isolated from faeces, although to detect virus by our method there must have been at least 50 TCD50/g. (Gardner *et al.*, 1960a). This suggested to us that, although these viruses are regarded as respiratory viruses, they must also have multiplied somewhere in the region of the alimentary tract, probably in the lymphatic tissue, as we did not believe faecal isolations resulted from faeces being contaminated by material swallowed from the upper respiratory tract. If this is accepted then it also follows that the site of multiplication could be the same as that favoured by the poliovirus. This immediately raises the question of whether such an adenovirus infection could result in interferon production (Isaacs and Lindenmann, 1957; Pereira, 1960) possibly, for example, interfering with poliovirus infection. In such cases the children who showed prolonged adenovirus excretion might have exhibited a non-specific resistance to other viruses, such as the poliovirus (Hale, 1961). Another surprising feature was the long-continued excretion of adenovirus, particularly type 5. It is possible that carriage of adenovirus is permanent or semi-permanent, its detection varying with the waxing and waning of an interferon-like substance in the bowel (Wagner, 1960). More studies are required into the length of virus excretion in different populations.

Adenoviruses were not mutually exclusive; simultaneous double type infection was found; on other occasions two children showed adenovirus type 5 excretion, but at a later date type 7 and type 6 were isolated

respectively, to be followed by adenovirus type 5 again. This must have been simultaneous double infection, and the laboratory result merely reflected that type 5 was normally dominant but occasionally the other types predominated. In a recent trial a similar picture was found when children were fed three types of poliovirus simultaneously (Hale *et al.*, 1961). One or two viruses would be isolated in the faeces, then the third would appear ; this was followed by the irregular reappearance of all types.

In spite of the frequency of isolation of adenovirus the general health of the community remained high. Mild coryzas were common, but never seemed to be related to the appearance of any adenovirus in the stools of those affected. Adenovirus type 7, an organism usually regarded as an epidemic strain, did not spread or produce clinical disease. This virus was introduced by a nurse in November, appeared in a toddler in December, and, after being excreted by a baby a month later, disappeared.

Adenovirus type 5 was isolated from no less than 50% of the children in the home, but never seemed to be responsible for any clinical illness with the possible exception of the outbreak of bronchiolitis described above. There are a number of hypotheses which might account for this outbreak. A new type 5 strain of virus may have been introduced during December which, when encountered by the very young and not the older children, caused respiratory illness ; alternatively, perhaps conditions at the time might have been such that if type 5 virus infection took place illness resulted. On the other hand, the bronchiolitis at this period might have been due to an agent undetectable by available methods, or to this agent in combination with adenovirus type 5 (Gardner *et al.*, 1960b). These cases, however, emphasize the difficulty in deciding the aetiology of a disease which may be due to a virological agent that can be carried by a large number of normal individuals showing no sign of disease.

As a result of a constant influx of new children and prolonged excretion by some residents, conditions for endemicity are established. Communities of this type, in which viruses are epidemic, may act as foci of infection for the general population.

Summary

A residential nursery has been studied over a period of a year for the excretion of adenovirus. Types 1–7 were found in stools, and in a number of children adenovirus type 5 was excreted for many months. Many children were capable of carrying more than one adenovirus, and the significance of this is discussed. The relationship of adenovirus excretion to the general health of the community is discussed, with special reference to an outbreak of bronchiolitis which occurred during the period of study.

We are indebted to Dr. C. Cooper, consultant paediatrician, the matron, and the staff for their co-operation.

REFERENCES

Berge, T. O., England, B., Mauris, C., Shuey, H. E., and Lennette, E. H. (1955). *Amer. J. Hyg.*, **62**, 283.
Gardner, P. S., McGregor, C. B., and Dick, K. (1960a). *Brit. med. J.*, **1**, 91.
—— Stanfield, J. P., Wright, A. E., Court, S. D. M., and Green, C. A. (1960b). Ibid., **1**, 1077.
Hale, J. H. (1961). *Advances in Immunology*. In press.
—— Lee, L. A., Gardner, P. S., and Lim, K. A. (1961). To be published.
Huebner, R. J., Rowe, W. P., Ward, T. G., Parrott, R. H., and Bell, J. A. (1954). *New Engl. J. Med.*, **251**, 1077.
Isaacs, A., and Lindenmann, J. (1957). *Proc. roy. Soc. B*, **147**, 258.
Jawetz, E., Kimura, S. J., Hanna, L., Coleman, V. R., Thygeson, P., and Nicholas, A. (1955). *Amer. J. Ophthal.*, **40**, No. 5, pt. 2, p. 200.
—— Thygeson, P., Hanna, L., Nicholas, A., and Kimura, S. J. (1956). *Proc. Soc. exp. Biol. (N.Y.)*, **92**, 91.
Morrison, B., Bass, D., Davis, J. A., Hobson, D., Madsen, T. I., and Masters, P. L. (1957). *Lancet*, **2**, 1077.
Munro-Ashman, D., Gardner, P. S., Taylor, C. E. D., and McDonald, J. C. (1958). Ibid., **2**, 121.
Pereira, H. G. (1960). *Virology*, **11**, 590.
Rowe, W. P., Huebner, R. J., Gilmore, L. K., Parrott, R. H., and Ward, T. G. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **84**, 570.
Wagner, R. R. (1960). *Bact. Rev.*, **24**, 151.

TABETIC GASTRIC CRISIS WITH FLUID LEVELS AND VISIBLE PERISTALSIS

BY

R. D. CATTERALL, M.R.C.P.Ed.

A. J. C. LATCHMORE, M.B.E., M.S., F.R.C.S.

AND

E. E. SHERWOOD-CUNDALL, M.B., Ch.B.

From St. James's Hospital, Leeds, and the General Infirmary at Leeds

Gastric crises are recurrent paroxysmal attacks of severe abdominal pain, with or without vomiting, occurring in patients suffering from tabes dorsalis. Their onset is usually sudden, and an attack may last hours, days, or weeks, and usually subsides rapidly and completely. The incidence of these attacks has declined during recent years with the decrease in cases of tabes dorsalis. However, the condition is still seen from time to time in different branches of medical practice, and the importance of considering the possible diagnosis of gastric crisis in patients complaining of severe abdominal pain cannot be stressed too frequently. Unnecessary surgical interventions in such patients occur so often that the presence of abdominal operation scars with pain has been alluded to by Tilney as one of the diagnostic signs of this syndrome.

The incidence of gastric crises in cases of tabes dorsalis appears to be about 12%. Bonar (1901), at Columbia University, found 36 cases of gastric crises among 286 cases of tabes dorsalis. Nuzum (1916) reviewed 1,000 cases of tabes and found that gastric crises were the initial symptom in 17%. The Cooperative Clinical Group in the United States (O'Leary *et al.*, 1938) studied 985 patients with tabes dorsalis, gastric crises occurring in 118.

The cause of gastric crises remains undetermined. Some authors regard the attacks to be of sympathetic origin. Others believe that they result from recurrent posterior ganglionitis in the lower dorsal segment of the cord. Others regard involvement of the vagus as responsible for the symptoms. Gowers (1900) showed that in cases of tabes with gastric crises there were marked lesions in the upper cervical segments of the cord. Eppinger and Hess (1917) regarded visceral crises as the outcome of irritation and later of paralysis of the autonomic nervous system. The only factors known to induce attacks are acute infection, emotional tension, and severe fatigue, but the majority occur

without obvious precipitating factors. Bennett (1925) thought that most crises occurred in the pre-ataxic stage of tabes.

The differential diagnosis of tabetic gastric crises includes a number of abdominal conditions. Peptic ulceration with or without perforation, gall-stones, cholecystitis, acute pancreatitis, appendicitis, renal colic, salpingitis, lead colic, peritonitis, and intestinal obstruction are the commonest intra-abdominal conditions which have to be considered. More rarely intrathoracic disease involving the diaphragmatic pleura, the pre-herpetic stage of herpes zoster, Henoch's purpura, acute porphyria, and dissecting aneurysm of the aorta have caused confusion.

There appears to be general agreement that the prognosis is usually good. Holmes (1906) stated that "as a rule attacks usually become less frequent and severe and eventually cease as the disease advances." O'Leary *et al.* (1938) reported that gastric crises disappeared after treatment in 44% and were less severe in 25%. In 7% crises became worse.

Few radiological studies of the gastro-intestinal tract during tabetic gastric crises have been reported. Schlesinger (1918) administered a barium enema to a patient during a severe crisis and observed marked spasm of the descending colon. Fremont-Smith and Ayer (1925) reported abnormal *x*-ray findings of the stomach in 15 out of 24 cases of gastric crisis. Five were shown to have organic lesions of the stomach, while in 10 the abnormalities were thought to be due to spasm. Patrick and Reeves (1953) reported one case of abnormality of the peristaltic activity of the stomach during a gastric crisis which disappeared when the crisis subsided. In a detailed study of the literature we have been unable to find a report of fluid levels being found on straight *x*-ray examination of the abdomen during gastric crises.

This paper describes a case of tabetic gastric crisis in which visible peristalsis was observed on abdominal examination and fluid levels were found on *x*-ray examination of the abdomen.

Case Report

The patient was a 49-year-old man who worked as a caretaker. In 1955 he had suddenly developed severe epigastric pain and vomiting. The symptoms disappeared spontaneously in 24 hours and he was told that they were due to gastroenteritis. Two years later the epigastric pain and vomiting recurred, lasting for five days. He was admitted to hospital and a diagnosis of peptic ulceration was made. A year after this—in 1958—he again complained of the sudden onset of severe upper abdominal pain with vomiting. He was admitted to hospital, where signs of tabes dorsalis were discovered. His blood Wassermann reaction was positive and the cerebrospinal fluid showed 84 lymphocytes per ml., 42 mg. of protein, a positive Wassermann reaction, and a Lange curve of 0011210000. *X*-ray examination of the chest showed that the heart and aorta were normal. He was given penicillin treatment and recovered from the crisis in six days. In 1959, or six months before we saw him, he had a further gastric crisis. A straight *x*-ray film of the abdomen and a barium meal during the crisis showed the stomach to be dilated and to contain fluid and a large air bubble. No fluid levels were seen in the intestines. He recovered spontaneously in eight days.

On further questioning it was found that the patient had frequent attacks of abdominal pain occurring every few weeks. These usually settled in a few days and did not require admission to hospital. His family doctor was in the habit of treating these attacks with pethidine.

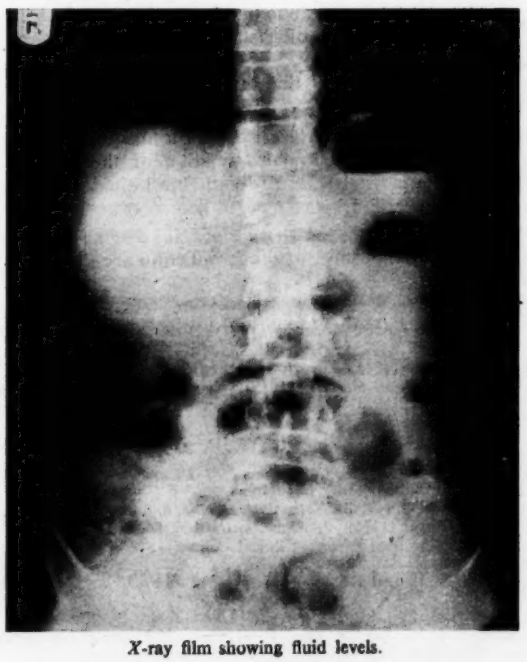
In 1960 the patient was admitted to St. James's Hospital, Leeds, with abdominal pain and vomiting of seven days' duration. He had received repeated injections of pethidine and morphine from his family doctor, but these had not given him any relief. The pain was colicky in nature, most severe in the umbilical region, and radiated up to the epigastrium. There were no aggravating factors, and the pain was eased with vomiting greenish fluid, this occurring frequently. Anorexia was almost complete, his bowel habit was normal, and he had passed flatus on the day of admission.

On examination he was crying out with pain and requesting surgical intervention. He was pale and sweating. There was no abdominal distension, tenderness, or guarding, although he held himself rigid at the peaks of pain. Bowel sounds were present and rectal examination revealed nothing abnormal. The pupils were irregular and unequal, and reacted sluggishly to light and briskly to accommodation. There was mild bilateral ptosis. The tendon reflexes were absent at both ankles and sluggish at the knees. The plantar responses were flexor and there had been evidence of posterior-column loss on previous examination, but at the time of admission his pain was so great that co-operation was not sufficient to test sensation efficiently.

At this time straight *x*-ray examination of the abdomen revealed numerous fluid levels in the small intestine but no evidence of gross dilatation (see Fig.). When this *x*-ray film was shown to several surgeons who did not know the history of the case they all advised immediate laparotomy.

A Ryle tube was passed and repeated enemas were given with good results. A fluid-balance chart was begun, but it was not thought necessary to give intravenous fluids.

Next day he was noted to have visible peristalsis in the region of the umbilicus, and bowel sounds were present and augmented in bouts corresponding with the peaks of pain. A further straight *x*-ray film of the abdomen was normal and the fluid levels had disappeared. No further visible peristalsis was observed. On the third day he was symptomless, but on the fifth day he had a slight relapse



X-ray film showing fluid levels.

of his pain. This was rapidly relieved by two injections of pethidine. He then made a speedy and complete recovery and has been well until the time of writing.

Discussion

Fluid levels in straight *x*-ray films of the abdomen are usually thought to indicate intestinal obstruction. Shanks and Kerley (1950) state that "the cardinal signs in plain films of intestinal obstruction are gas-distended coils of gut and fluid levels." The finding of visible peristalsis on abdominal examination makes the diagnosis of subacute intestinal obstruction even more probable. However, in this case the fluid levels had disappeared when the abdomen was *x*-rayed 24 hours later and the visible peristalsis was not observed again. The patient has been symptom-free and in good health for six months since this episode.

The course of the illness, with the sudden disappearance of the physical signs and the complete symptomatic recovery, suggests that the cause of the subacute obstruction was a reversible process. Severe localized spasm of the intestine appears to be the most likely explanation. Spasm of the large intestine and of the stomach and pylorus has been noted by previous observers (Schlesinger, 1918; Fremont-Smith and Ayer, 1925). Moreover, relief of symptoms in gastric crisis can often be obtained by giving atrophic sulphate intravenously (Alajouanine and Horowitz, 1932). The evidence therefore suggests that the fluid levels seen on the *x*-ray film of the abdomen were caused by intestinal spasm. A similar mechanism is probably responsible for the visible peristalsis, the vomiting, and, in some degree, for the abdominal pain.

Cases of tabetic gastric crises are sometimes seen in casualty departments and in surgical services where straight *x*-ray examination of the abdomen is often carried out routinely on all patients with acute abdominal pain. Attention is drawn to the fact that the finding of fluid levels on the *x*-ray film and of visible peristalsis on abdominal examination does not exclude the diagnosis of gastric crisis.

Summary

A patient known to have tabes dorsalis and to have suffered previous gastric crises was found to have fluid levels on straight *x*-ray examination of the abdomen and visible peristalsis on abdominal examination during a severe gastric crisis.

The significance of these signs in diagnosis and a possible mechanism for their production are discussed.

REFERENCES

Alajouanine, T., and Horowitz, A. (1932). *J. Méd. Paris*, **52**, 380.
Bennett, A. E. (1925). *Amer. J. med. Sci.*, **170**, 538.
Bonar, A. B. (1901). *J. nerv. ment. Dis.*, **28**, 259.
Eppinger, H., and Hess, L. (1917). *Vagotonia: Clinical Study in Vegetative Neurology*, 2nd ed. Nervous and Mental Diseases Publishing Co., New York.
Fremont-Smith, M., and Ayer, J. B. (1925). *J. Amer. med. Ass.*, **85**, 1282.
Gowers, W. R. (1900). *A Manual of Diseases of the Nervous System*. Blakiston, Philadelphia.
Holmes, G. M. (1906). *Nelson's Medicine*, **6**, 401.
Nuzum, J. W. (1916). *J. Amer. med. Ass.*, **66**, 482.
O'Leary, P. A., *et al.* Clinical Cooperative Group (1938). *Vener. Dis. Inform.*, **19**, 367.
Patrick, S. I., and Reeves, R. J. (1953). *Arch. intern. Med.*, **92**, 920.
Schlesinger, E. (1918). *Verh. Berl. med. Ges.*, **49**, 190.
Shanks, S. C., and Kerley, P. (1950). *A Textbook of X-ray Diagnosis*, 2nd ed., **3**, 298. Lewis, London.

Preliminary Communications

Haptoglobin Types in Natives from the Kuru Region and Other Parts of Melanesia

At an early stage in the study of the fatal neurological disorder kuru among Fore natives in the Eastern Highlands of Australian New Guinea, Bennett, Rhodes, and Robson (1958, 1959) reported the occurrence of distinctive family patterns in respect of the incidence of the disease. After a detailed examination of the family data which had been obtained by Robson and Rhodes during their field investigations in January, 1958, I was led to put forward very tentatively, and as basis for further study, a single gene model for kuru (Bennett *et al.*, 1958, 1959). This suggestion was that kuru might be under the control of autosomal alleles *Ku* and *ku* such that, in females, homozygotes *KuKu* and heterozygotes *Kuku* would be potential early-onset and late-onset victims respectively, while in males the homozygotes *KuKu* would be potential kuru victims with the heterozygotes clinically normal. Such a possible genetic basis for kuru, though rather improbable from some points of view, was formally consistent with the immediate family data available.

Extensive field studies carried out subsequently have shown that the distinctive family patterns in respect of this disease occur generally in the kuru region (Bennett, Gray, and Auricht, 1959). It is not certain, however, that the familial nature of kuru has its only explanation in this genetical basis. Other possible explanations —for example, a toxic factor with a familial component —must be borne in mind. In the present state of knowledge it is particularly important, therefore, to seek data of a type that may furnish a critical test of this genetical hypothesis.

In this connexion, the report by Curtain (1959) of a marked association of kuru with the haptoglobin gene Hp^2 appeared worthy of attention, for it seemed to me that it would be very difficult, if not impossible, to reconcile such an association with the genetical model for kuru. Consequently, it was important to carry out an independent test for this association. This has been done and the results have been placed on record (Bennett, Auricht, Gray, Kirk, and Lai, 1961). Our material did not give any support to the suggested association; the frequencies of the haptoglobin types in kuru victims and in the other Fore natives without kuru chosen for comparison were almost identical.

Curtain, Gajdusek, and Zigas (1961) have now reported their work in some detail and have included results of the retyping by Dr. R. L. Kirk, of Perth, of some of their original sera from kuru victims for the haptoglobins. There is no longer any significant difference in the values for the frequency of the Hp^2 gene in their kuru and "normal" groups, and the gene frequencies which they give are in fact close to those reported by Bennett *et al.* (1961). Though these gene frequencies are close together, however, there are very marked differences between the frequencies of the three haptoglobin types reported by Curtain *et al.* and those given by Bennett *et al.* Both series of typings are summarized in Table I. It also includes the haptoglobin frequencies for a further group of 29 "normal" Fore individuals typed recently in this laboratory by D. W. Cooper, using the method of vertical starch-gel electro-

phoresis with the discontinuous trisborate system of M. D. Poulik. (Some of the weaker haptoglobins were checked in borate buffer. Two female individuals who were classified as *Hp* 0–0 have been omitted from the Table.) The difference between the frequencies of the haptoglobin types given in the two parts of Table I is highly significant, the value of χ^2 with two degrees of freedom testing for proportionality being 8.9 (P=0.01).

In considering how such large differences might be accounted for, it is instructive to compare the reported frequencies for the haptoglobin types with the expectations which can be calculated from the given gene frequencies, assuming random mating. These expectations are shown in parentheses in Table I. It can be seen from the values of χ^2 (with 1 D.F.) testing for agreement between the observed and expected frequencies that, whereas the data of Bennett *et al.* are in close agreement with the expectations, the records of Curtain *et al.* show very significant departures from the expectations, with striking deficiencies in the recorded frequencies for the heterozygote *Hp* 2–1. Deficiencies of this kind may result from a number of causes. For example, if the haptoglobin type frequencies varied greatly through the kuru region, pooling of data obtained in different parts could show a deficiency of heterozygotes. However, there is nothing in our data referring to haptoglobin, and also to transferrin types and blood groups, to suggest either a departure from random mating frequencies or that there is very much variation in these gene frequencies in the Fore region. Again, unrepresentative selection either of individuals in the field for bleeding or of blood samples in the laboratory for typing could lead to the discrepancies described. A tendency to choose individuals from small inbred groups, for example, could account for a deficiency of heterozygotes. It may be noted that if this should be the correct explanation, the reliability of the data reported by Curtain *et al.* for quantitative differences in the serum proteins in this New Guinea population would also be open to question. This is because one result of such biased selection of blood samples could be that the within-group variation is underestimated and the significance of differences between groups overstated.

Another possible explanation for the discrepancies described is that Curtain *et al.* made a systematic error in technique. It is therefore of interest to examine, in the same way as above, the haptoglobin typings they have reported for other populations. These data and the corresponding random mating expectations are shown in Table II. For each population, their typings show a deficiency of the heterozygous type *Hp* 2–1 and an excess of the two homozygous types *Hp* 1–1 and *Hp* 2–2. In many cases these discrepancies are rather large. Curiously enough, the only group for which their typings do not show a relatively large deficiency of heterozygotes is that described as "Australian Blood Bank donors; patients attending Alfred Hospital, Melbourne." This would appear to be the only group where the authors have not effected the selection of the individuals included for typing.

Examination of the blood-group data for these groups of individuals may throw further light on this problem. In any event, the presence of the large discrepancies described, whatever their cause, prevents us from having confidence in these haptoglobin typings presented by Curtain *et al.* Simple biometrical tests carried out as such typings are proceeding should avoid similar wastage in future work of this kind.

TABLE I.—*Haptoglobin Types of Kuru Patients and "Normal" Fore Individuals. Expectations are Shown in Parentheses*

	Haptoglobin Type				Gene Frequency		χ^2_1	Probability
	1–1	2–1	2–2	Total	Hp^1	Hp^2		
Data of Curtain et al. (1961)								
Kuru patients	31 (25·3)	28 (39·4)	21 (15·3)	80	0·56	0·44	5·55	0·043
"Normal" Fore	31 (25·1)	17 (28·6)	14 (8·2)	62	0·64	0·36	8·59	0·003
Total	62	45	35	142	0·60	0·40		
Per cent.	43·7	31·7	24·6					
Data of Bennett et al. (1961) and New Material								
Kuru patients	21 (20·5)	20 (21·1)	6 (5·4)	47	0·66	0·34	0·002	0·962
"Normal" Fore	16 (15·7)	15 (15·5)	4 (3·8)	35	0·67	0·33	0·017	0·897
" Fore*	10 (11·1)	16 (13·7)	3 (4·2)	29	0·62	0·38	0·281	0·605
Total	47	51	13	111	0·65	0·35		
Per cent.	42·3	45·9	11·7					

* New material.

TABLE II.—*Haptoglobin Types for Various Populations Reported by Curtain et al.* (1961). *Expectations are Shown in Parentheses*

	Haptoglobin Type				Gene Frequency		χ^2_1	Probability
	1–1	2–1	2–2	Total	Hp^1	Hp^2		
Gimi-Mane	14 (11·1)	6 (11·8)	6 (3·1)	26	0·65	0·35	4·27	0·039
Kukukuku-Menyamya	20 (17·0)	30 (36·0)	22 (19·0)	72	0·49	0·51	1·38	0·241
Chimbu	16 (12·3)	9 (14·3)	9 (5·4)	34	0·60	0·40	5·06	0·025
Bougainville	15 (12·9)	8 (12·2)	5 (2·9)	28	0·68	0·32	1·94	0·165
Pacific Islands Regiment	12 (8·5)	4 (11·0)	7 (3·5)	23	0·61	0·39	6·80	0·009
Peruvian Amazon shore residents	13 (7·3)	9 (20·4)	20 (14·3)	42	0·42	0·58	10·93	0·001
White Australians	46 (43·8)	116 (120·4)	85 (82·8)	247	0·42	0·58	0·20	0·661

J. H. BENNETT, M.A., B.Sc., Ph.D.,
Department of Genetics,
Adelaide University, South Australia.

REFERENCES

Bennett, J. H., Auricht, C. O., Gray, A. J., Kirk, R. L., and Lai, L. Y. C. (1961). *Nature (Lond.)*, **189**, 68.
—— Gray, A. J., and Auricht, C. O. (1959). *Med. J. Aust.*, **2**, 505.
—— Rhodes, F. A., and Robson, H. N. (1958). *Aust. Ann. Med.*, **7**, 269.
—— —— —— (1959). *Amer. J. hum. Genet.*, **11**, 169.
Curtain, C. C. (1959). *Aust. J. Sci.*, **22**, 167.
—— Gajdusek, D. C., and Zigas, V. (1961). *Amer. J. trop. Med. Hyg.*, **10**, 92.

Cyproheptadine in Treatment of Urticaria

Cyproheptadine (" periactin ") is a new antihistamine and antiserotonin drug. Its structure is 1-(1:2-5:6-dibenzo*cyclo*heptatrienylidene) - 4 - methylpiperidine hydrochloride monohydrate. In animal experiments it antagonizes the bronchoconstrictor effect of serotonin, the ability of serotonin to increase capillary permeability, and the bronchoconstrictor, vasodepressor, and spasmogenic effects of histamine. It protects against active and passive anaphylaxis. Chronic toxicity studies show no ill effect which would prevent its use in man (Merck Institute for Therapeutic Research, 1958).

Histamine is known to be implicated in the pathogenesis of allergic reactions and serotonin is thought to be an important additional factor in some species, but very little is known of the significance of serotonin in allergic reactions in man (Jensen, 1960). We thought that as cyproheptadine is both an antihistamine and an antiserotonin it might be useful in the treatment of allergic disorders. A preliminary trial in patients attending the allergy clinic at the Manchester Royal Infirmary showed that cyproheptadine was strikingly effective in three out of five patients with chronic urticaria when given in dose of between 2 and 6 mg. daily, whereas it was ineffective in five out of seven patients with bronchial asthma and only partially effective in the other two despite doses of up to 30 mg. daily. No ill effect of the drug was encountered, and in view of its apparent success in urticaria we decided to test its effectiveness in a double-blind trial against a dummy lactose tablet.

METHOD AND TRIAL

Twenty-seven patients suffering from chronic urticaria were chosen from a larger group attending the allergy clinic at the Manchester Royal Infirmary. All had urticaria more often than once weekly but with little change in frequency in the period before the trial. Most had been referred because of failure to respond to antihistamine therapy. Each patient kept a record of the number and duration of attacks during a two-week period before introduction into the trial. Cyproheptadine (2-mg. tablets) and an identical lactose dummy were dispensed by the hospital pharmacist on a random allocation, and neither patient nor physician knew which tablet had been issued. The patient was instructed to take one tablet three times daily, to keep a record of the attacks, and to note any side-effects of the tablet.

The results were assessed at the end of two weeks. In most instances the patient was then given the alternative tablet for a further two weeks and at the end of this time the results were compared. If there had been no success with either tablet the trial was continued using active or dummy 5-mg. tablets. The result was classified as excellent if there had been complete control of urticaria, improved if there had been a reduction in the number of attacks, and failure if there had been no change. After the final assessment had been made on each patient the key was opened and the identity and order of the tablets given to each was discovered.

RESULTS

Two patients failed to attend for follow-up. Of the 25 who completed the trial, 22 had been treated with both kinds of tablet. The results are shown in the Table.

Results of Treatment

Result	No. on Cyproheptadine	No. on Dummy
Excellent	16	0
Improved	5	0
Failure	4	22

An excellent response was obtained in 15 patients on 2 mg. of cyproheptadine three times daily and in one patient on 5 mg. three times daily. Four of those who showed improvement were given cyproheptadine 5 mg. three times daily. The fifth improved on 2 mg. three times daily but suffered drowsiness and the dose was not increased.

One patient discontinued treatment while on 2 mg. of cyproheptadine three times daily because of drowsiness. Two other patients complained of drowsiness on 2 mg. three times a day but this was soon overcome and treatment continued without side-effect.

DISCUSSION

The results show that cyproheptadine is effective in urticaria, and we believe that it will find a place in the management of this condition. Others have reported similar findings in urticaria and have found the drug useful in other conditions. Bodi *et al.* (1961), in an open trial, found that cyproheptadine led to marked improvement in three out of four patients with urticaria and in two patients with angioneurotic oedema, marked or moderate improvement in 10 out of 14 patients with rhinitis, but little improvement in 14 patients with asthma.

Kaminsky and Asrilant (1960) studied 17 patients with urticaria and found an excellent or very good response in 14 on an average dose of 10 mg. daily; they also found that the drug might help patients with eczematoid dermatitis and pruritus. Miller and Fishman (1961) treated seven patients with urticaria and found an excellent response in two and a good response in three. Some patients with hay-fever and recurring headache responded to cyproheptadine, but only a few with asthma obtained relief. Welsh and Ede (1961) showed that cyproheptadine was an effective antipruritic in an optimal dose of 15 to 20 mg. daily and that only seldom was drowsiness experienced. Jensen (1960) found that 10 mg. of cyproheptadine controlled the skin reaction to grass-pollen extract and that in a dose of as little as 2.5 mg. it was more effective than 30 mg. of phenindamine hydrogen tartrate (" thephorin ").

Our experience suggests that it is seldom necessary to use more than 6 mg. of cyproheptadine daily in order to control urticaria. Follow-up over a period of up to six months has shown that most patients remain well on a daily maintenance dose of 2 mg. or on occasional use of the tablets.

SUMMARY

A controlled double-blind trial of cyproheptadine in 25 patients with urticaria has shown that the drug is effective in a dose of 6 mg. daily. Side-effects were minimal and unimportant.

I am grateful to Dr. W. Brockbank for his help and advice; to Mr. J. B. Lloyd, chief pharmacist, Manchester Royal Infirmary, for his help with the trial; and to Merck Sharp and Dohme Ltd. for the supply of cyproheptadine (periactin) and dummy tablets.

I. S. BAILEY, M.D., M.R.C.P.,
Senior Registrar in Medicine, Manchester Royal Infirmary.

REFERENCES

Bodi, T., Siegler, P. E., Brown, E. B., Gershenfeld, M. A., and Nodine, J. H. (1961). *Ann. Allergy*, **19**, 386.
Jensen, K. (1960). *Acta allerg. (Kbh.)*, **15**, 293.
Kaminsky, A., and Asrilant, M. (1960). *Dia méd.*, **32**, 1970.
Merck Institute for Therapeutic Research (1958). Cyproheptadine: Preclinical Evaluation.
Miller, J., and Fishman, A. (1961). *Ann. Allergy*, **19**, 164.
Welsh, A. L., and Ede, M. (1961). *J. new Drugs*, **1**, 22.

Rapid Serological Diagnosis of an Outbreak of Influenza

The laboratory diagnosis of virus infection of an individual patient generally requires either isolation and identification of the virus or demonstration of rising titres of antibody in paired sera collected in the early acute stage (first week) and in the later, convalescent stage (third week) of illness. Examination of single sera is rarely helpful, since blood collected early during infection will not contain antibody, while the mere finding of antibody in a single later sample does not indicate when the antibody developed, and cannot prove temporal or causal relationship between the corresponding infection and the illness in question. For these reasons the virus laboratory is often unable to provide specific diagnosis except in retrospect.

In the case of an outbreak, however, it is sometimes possible to make a rapid serological diagnosis by examination of single sera collected from patients with typical illness for the shortest and longest available times, with not less than 6 or preferably 12 in each group. It is desirable that the "short-duration" group includes patients who sickened on the day of blood collection, and that the "long-duration" group includes some who have been ill for at least one week. The sera can be tested within 24 hours of receipt at the laboratory, and the diagnosis of the outbreak may be revealed by comparison of the titres of the "short-duration" and "long-duration" groups. It should be noted that symptomless individuals are unsuitable for this type of investigation because silent but immunizing infections are not uncommon in outbreaks of virus infection.

This method of diagnosing an outbreak may be useful to the medical officer in charge of a group of persons such as factory workers, schoolchildren, personnel of a military unit, or patients in a hospital community. The purpose of this paper is to illustrate the procedure by describing its application to an outbreak of influenza in a geriatric unit during the A2/Asian epidemic of spring, 1961.

DESCRIPTION OF OUTBREAK

Early in February, 1961, a few elderly men in a long-stay geriatric hospital simultaneously developed an acute illness with pyrexia of about 100° F. (37.8° C.), rigors, malaise, bone pains, and a dry cough. Similar illnesses appeared in small crops a few days later among other patients in the same ward and in two adjacent wards. Approximately 20% of the population at risk suffered from the illness. Most cases were of moderate severity, and the patients recovered after five to seven days, though they remained debilitated for some weeks. A few patients suffered severe respiratory complications, and one man with chronic cardio-respiratory disease died in the acute phase of the illness.

INVESTIGATION OF OUTBREAK

Blood specimens were collected from 14 patients on February 7, 1961. Sera were separated and subjected to a screening test at a single dilution (1/8) by complement fixation against a series of respiratory virus antigens. Those which gave positive reactions were then tested in twofold serial dilutions to determine their titres. The results are summarized in the Table, together with tests of second sera collected from the same patients with the exception of the one fatal case. The cases are listed in order of duration of illness at the time of the first bleeding.

Antibody Titres of Sera Tested Against Six Virus Antigens

Case No.	First Sera							Second Sera						
	Day of Illness	A	B	C	Ad	P	Q	Day of Illness	A	B	C	Ad	P	Q
1	1	8	0	0	0	0	0	21	512	0	0	0	0	0
2	1	8	0	0	0	0	0	21	32	0	0	0	0	0
3	2	8	16	8	0	0	0	22	16	0	0	0	0	0
4	2	8	0	0	0	0	0	22	256	0	0	0	0	0
5	2	8	8	0	0	0	0	22	512	8	0	0	0	0
6	2	8	0	0	0	0	0	—	—	—	—	—	—	—
7	4	8	0	0	0	0	0	24	512	0	0	0	0	0
8	4	8	0	0	0	16	0	14	64	0	0	0	16	0
9	4	8	0	0	0	0	0	14	256	0	0	0	0	0
10	6	8	0	0	0	0	0	26	128	0	0	0	0	0
11	6	0	0	0	0	0	0	16	16	0	0	0	0	0
12	7	16	0	0	0	0	0	17	256	0	0	0	0	0
13	7	64	0	0	0	0	0	17	256	0	0	0	0	0
14	10	256	0	0	0	0	0	20	256	0	0	0	0	0

A = Influenza A. B = Influenza B. C = Influenza C. Ad = Adenovirus. P = Psittacosis. Q = *Rickettsia burneti*. 0 = Less than 8.

The Table shows that in most cases antibodies were not detected to influenza B and C, adenovirus group, psittacosis group, or *R. burneti* (the causal organism of Q fever). Only Cases 3, 5, and 8 had low antibody titres (8–16) to influenza B, influenza C, or psittacosis, and these results were not associated with longer durations of illness. On the other hand, every case except one had type A influenza antibody detectable in the first serum. Most of these titres were low, presumably residual from infections in earlier life, but the three cases whose first sera were withdrawn on the seventh or later day of illness showed titres of 16, 64, and 256 respectively. This concentration of significantly higher titres among cases with the longest duration of illness justified a provisional diagnosis of influenza A virus as the cause of the outbreak. The availability of this presumptive diagnosis as soon as the second crop of illnesses occurred was of great service in the clinical management of the hospital outbreak. The diagnosis was subsequently confirmed by the rising titres to influenza A but not to other virus antigens shown by tests of second sera collected from the same patients.

SUMMARY

The cause of an outbreak of suspected virus infection may often be revealed by serological examination of blood sera collected on one occasion from patients with different durations of illness. This method was successfully used for the early rapid diagnosis of an outbreak of influenza in a geriatric hospital.

N. R. GRIST, M.B., B.Sc., F.R.C.P.Ed.,
Lecturer in virology, University of Glasgow.

J. KERR, A.I.M.L.T.,
Senior Technician, University Department of Virology, Ruchill Hospital, Glasgow.

B. ISAACS, M.D., F.R.F.P.S., D.Obst.R.C.O.G.,
Assistant Physician, Foresthall Hospital, Glasgow.

Medical Memoranda

A Case of Primary Peritoneal Pregnancy

Owing to its extreme rarity, primary peritoneal pregnancy was not generally recognized as a clinical entity until 1942, when Studdiford, in a case report, settled the question beyond doubt. Before a sure diagnosis may be made, he suggested the following criteria: (1) that both tubes and ovaries are normal, with no evidence of recent pregnancy; (2) the absence of any evidence of a utero-peritoneal fistula; and (3) the presence of a pregnancy related exclusively to the peritoneal surface and young enough to eliminate the possibility of secondary implantation after a primary nidation in the tube.

The following case satisfies all three criteria. At the time of admission the period of gestation could not have been much longer than 25 days, and this accords well with the small gestational nodule of 1.5 cm. diameter. At the time of operation it was not fully appreciated that the case was in fact one of primary peritoneal implantation. Vital evidence in a minute piece of tissue from the gestation sac enabled the rare diagnosis to be made.

CASE REPORT

A Chinese woman aged 35, para-4, was admitted to the Kandang Kerbau Hospital, Singapore, on September 26, 1959, with severe abdominal pain of three hours' duration. The pain had started in the epigastrium and rapidly spread to the flanks. She fainted once at home and again on arrival at the hospital. The last menses began on August 16, 41 days before admission. Her periods were always regular, 3–4 days every 28–30 days. Her last confinement was two years previously.

On examination the patient was in a state of collapse. The blood-pressure was 85/50 mm. Hg and the pulse rate 120 a minute. The abdomen was very tender to palpation and marked shifting dullness was present.

The uterus was normal in size and position. The cervix was very tender to palpation but not obviously softened. The lateral and posterior fornices were also very tender. There were no adnexal masses. A diagnosis of ruptured ectopic pregnancy was made.

Immediate laparotomy via a subumbilical midline incision revealed the presence of 3 pints (1.7 litres) of blood and clots in the peritoneal cavity. The uterus, tubes, and ovaries appeared perfectly healthy. There was a corpus luteum in the left ovary. As much blood as possible was removed from the peritoneal cavity, but more fresh blood seemed to be issuing from within the abdomen. The abdominal incision was extended upwards to facilitate a thorough search for he source of bleeding. The liver, spleen, and kidneys were normal and intact. The bowels were then systematically inspected. Four feet (1.2 metres) from the ileo-caecal junction was a haemorrhagic nodule, about 1.5 cm. in diameter, on the ileum near its mesenteric border (Fig. 1). A pulsating mesenteric artery was spurting blood from a small rupture in the nodule.

FIG. 1.—Sketch showing loop of ileum with implantation site as seen at operation.

FIG. 2.—Section showing early chorionic villi from operation specimen. (H. and E. ×63.)

On close scrutiny the nodule contained what appeared to be a small piece of placental tissue. This was saved for histological examination. The bleeding-point was controlled and the raw area on the ileum repaired with an atraumatic suture. The patient was given 3 pints (1.7 litres) of blood. Convalescence was uneventful. She menstruated for the first three days and returned home on the eighth day.

Pathological Report.—The tissue on section showed areas of blood clot and chorionic villi (Fig. 2).

I thank Dr. E. K. Koh for his sketch (Fig. 1) and the Director of Medical Services, Singapore, for permission to publish.

S. H. Tow, M.R.C.O.G.,
Lecturer in Obstetrics and Gynaecology, University of Malaya in Singapore, Kadang Kerbau Hospital for Women, Singapore.

REFERENCE

Studdiford, W. E. (1942). *Amer. J. Obstet. Gynec.*, **44**, 487.

The medical research committee of the National Deaf Children's Society has drawn up a research programme of the most urgent problems which need investigation and which the Society is prepared to support. It includes research into the following: causes of congenital deafness; certain aspects of prevention of deafness; improved methods of testing the hearing of small children; the rehabilitation of the deaf child; the best type of amplifying system in the home; and acoustic conditions in schools, classrooms and halls, and rooms in which routine school audiometry is carried out. An early opportunity will be taken to bring together for informal discussion research workers in the various aspects of the subject. The membership of the medical research committee is now as follows: Mr. I. G. ROBIN *(chairman)*, Mr. J. CHALMERS BALLANTYNE, Mr. S. MAWSON, Mr. M. PARSONS, Dr. L. FISCH, and Mr. M. REED, B.Sc. (all of London); Dr. J. FULTON CHRISTIE (Glasgow); Mrs. FLORENCE CAVANAGH (Manchester); Mr. GAVIN LIVINGSTONE and Mr. R. G. MACBETH (both of Oxford); Mr. R. HUNT WILLIAMS (Reading).

Reviews

HUMAN NUTRITION

Recent Advances in Human Nutrition. With Special Reference to Clinical Medicine. By J. F. Brock, D.M.(Oxon.), F.R.C.P.(Lond.) (Pp. 454+xii; illustrated. 50s.) London: J. and A. Churchill Ltd. 1961.

A recent development in the production of medical and other technical books, doubtless engendered by the wealth of information to be imparted and the rapidity of progress, has been a rise in the importance of the editor at the expense of the individual author. Sometimes the editor can enjoy the prestige of having his name on the cover of a book by persuading a sufficient number of experts to contribute sections on their special fields, while himself limiting his labours to amending and arranging the texts submitted to him. Dr. Brock can claim to have written by himself about one-third of this interesting and instructive book. This is a praiseworthy effort in dealing with recent advances, which do not allow the writer to take his time for a leisurely and comprehensive survey of his whole subject. In 18 chapters on a "general review of trends" he covers topics such as food, calories, and nutrients; malabsorption syndromes; food additives and residues; recommended allowances; and infant feeding. Signs of hasty writing may be found in a chapter on "carbohydrates, vitamins, trace and other minerals" in which Dam, Woollam, and Gerber have become Bam, Wollan, and Gerba respectively, and in which the absorption band of vitamin A has been changed from 328 to 238 mμ. In a section on vitamin E, too brief to be really helpful, no mention is made of the important research on human volunteers by Horwitt. A sentence without a verb on page 90, however, suggests that an allusion to this work may perhaps have been missed out during typing or printing. Such minor imperfections, however, will detract but little from the value of a stimulating review of progress, to which much careful thought has obviously been devoted.

Of the 14 invited contributions, five have come from Brock's colleagues in South Africa, four from the U.S.A., three from Great Britain, and one each from France and Germany. B. Bronte-Stewart has written on dietary fats, with special reference to the effects of different kinds of fat on blood cholesterol and heart disease. Various aspects of protein requirements have been discussed by J. D. L. Hansen and by B. S. Platt. N. S. Scrimshaw deals with nutrition and infection, and A. W. Woodruff with nutritional anaemia in the tropics. A chapter by W. P. U. Jackson on the effect of nutrition on the skeletal system includes a lucid discussion on the calcium requirements of man. P. Gyorgy reviews bacterial symbiosis, including the role of dietary factors in stimulating the growth of *L. bifidus* in the intestines of the normal breast-fed infant. Dr. Brock must be congratulated on obtaining the help of such distinguished colleagues, and for producing a book which nobody interested in human nutrition can afford to miss.

T. MOORE.

BERLIN CARCINOGENESIS SYMPOSIUM

Berliner Symposion über Fragen der Carcinogenese. Edited by Professor Dr. H. Kraatz, Professor Dr. A. Graffi, Professor Dr. H. Gummel. Revised by Dr. H. Bielka. (Pp. 366 +x; illustrated. No price.) Berlin: Akademie-Verlag. 1960.

The collected papers and discussions of a symposium held in Berlin in December, 1959, on the problem of carcinogenesis make one think that, if this pathological process, triggered off by a great number of agents, had been completely elucidated by now, the fundamental nature of cancer, at least that of its cause, would be an open book to everybody. This would be not only a matter of enormous intellectual satisfaction, but, even more important, of immense practical value.

In place of such a solution of this problem there exists only a slow progress in finding small answers here and there. That is why an overall assessment has to be made from time to time and a number of workers in this field called together from all over the world so that they can learn from each other what it looks like a small distance away from their own preoccupation, or even on the other side of the hill. This can be done by different means, but one of the most fashionable is that of a symposium, especially on an international basis, Because of lack of space in the auditorium and the distances to be travelled, not all workers in the field are able to assemble together, but merely a representative portion of them. Consequently, if their deliberations are prepared for print and finally issued in the form of a volume, those who could not be present or people who have a general interest in the topic have a chance to learn of the results, however intermediate in character they may be.

The German Academy of Sciences in Berlin has done just that, and the book in front of us gives everybody a very good idea of how far the attempts to solve the problem under discussion have travelled.

Such topics as exogenous and endogenous carcinogenic substances, initiators, and promoters; the effect of polymers and ionizing radiation; the role of tobacco smoke and air pollution, of viruses and subcellular particles, have all been given ample time and attention for review and discussion.

For those of us whose linguistic skill is small, it is rather difficult to guess at the Russian contributions, and for some of us the German and French discussion remarks are difficult too. During the meeting itself translations must have been made available to the audience, but the readers of the printed edition do not have this advantage even in a condensed form. Nevertheless the volume will be of great use in the meantime, and certainly as a basis for further consideration of the problem in the not-too-distant future.

F. BERGEL.

GEOFFREY KEYNES

Geoffrey Keynes. Tributes on the Occasion of his Seventieth Birthday, with a Bibliographical Check List of his Publications. (Pp. 64; illustrated. No price.) London: Published for the Osler Club of London by Rupert Hart-Davis Ltd. 1961.

On March 25, 1957, Sir Geoffrey Keynes celebrated his seventieth birthday. On the following day, to mark the occasion, the Treasurer and Governors of St. Bartholomew's Hospital entertained him and a gathering of his friends at tea in their Great Hall, where tributes were paid to him by Sir Russell Brain and others. In the evening Sir Geoffrey was the guest of the Osler Club, where Sir Gordon Gordon-Taylor in an eloquent speech and Dr. A. W. Franklin felicitously voiced the Club's congratulations. Dr. W. S. C. Copeman, the President, presented to Sir Geoffrey a portrait drawing by Mr. Gilbert Spencer. This slim volume records these tributes, and there is a valuable bibliography of Sir Geoffrey's writings on surgery, archaeology, and general literature by Mr. W. R. LeFanu.

Distinguished as a surgeon—*inter alia*, his pioneer work in blood transfusion laid the foundations of the Blood Transfusion Service, which has saved countless lives—Sir Geoffrey is equally famous as a man of letters, a bibliographer, an authority on William Harvey, Sir Thomas Browne, William Blake, Samuel Butler, and John Donne. To no other in our time could Dr. Johnson's encomium of Goldsmith be more aptly applied: *Nullum quod tetigit non ornavit.*

ARTHUR S. MACNALTY.

THE LYMPHOCYTE

The Lymphocyte and Lymphocytic Tissue. By 21 Authors. Edited by John W. Rebuck, M.D., Ph.D. (Pp. 312+xi; illustrated. No price.) New York: Paul B. Hoeber, Inc. 1960.

This book contains nineteen lectures delivered at a course sponsored by the International Academy of Pathology and held in Boston in 1959. The authors are all from hospitals and research centres in the U.S.A., and their contributions give impressive testimony of the enthusiasm and skill devoted to haematological research in that country. A few years ago the lymphocyte could still be dismissed, in texts of physiology and pathology, as of virtually unknown function. Now we have a monograph packed with details of structure, ultrastructure, cytochemistry, and a multiplicity of functional activities of this remarkable cell. The tide of interest which began perhaps with Metchnikoff's studies of lymphocyte migration and transformation in inflammatory states more than 70 years ago has grown to a flood in recent years with the introduction of powerful new means of research, and this book illustrates vividly how rapidly knowledge has grown. The monograph is in no sense definitive; the constituent chapters are reviews of current knowledge, which already call for occasional correction and supplementation. But, considered as an interim review of a fast expanding field, the book is excellent. It contains a wealth of data, and much speculation, on the origins, transformations, and interrelationships of lymphocytic cells, their life span and turnover, their chemical composition, their role in antibody formation, in tissue transplantation, and in inflammations, their response to adrenocortical steroids and to radiation, and their involvement in neoplastic and proliferative diseases. The individual chapters are supplemented with full bibliographies, and are adequately illustrated with charts, tables, and half-tone photographs. The work is recommended with confidence to all who are interested in the lymphocyte.

F. G. J. HAYHOE.

MANUAL OF DERMATOLOGY

Dermatology. Diagnosis and Treatment. By Marion B. Sulzberger, M.D., F.A.C.P., Jack Wolf, M.D., Victor H. Witten, M.D. With the collaboration of Alfred W. Kopf, M.D. Second edition. (Pp. 615; illustrated. £5 5s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers Ltd. 1961.

The first edition of this work has for many years had a deservedly high reputation among dermatologists and practitioners. The present edition of this attractive handbook is welcome and is largely rewritten to present the modern approach to treatment of common skin diseases.

The authors give broad and detailed consideration to the principles of diagnosis and of topical medication in 80 pages of text, which are well illustrated, before passing to the diagnosis and treatment of common skin diseases. There is also a valuable chapter on antibiotics and steroid therapy, but steroids are used more freely than is the practice with dermatologists in Great Britain. The text is lucid and practical, and the general advice to use few remedies but to know all there is to know about them is sound, though it becomes more difficult to follow every day. Some elaborate and old-fashioned remedies of doubtful value still find a place, but that is not displeasing. Less welcome are the many proprietary remedies which are not universally available. It is surprising that antihistamine and anaesthetic applications are countenanced even though warning of their high sensitizing qualities is stressed. That must evidently reflect the experiences of the authors.

There are a few coloured plates, but most of the illustrations are in black-and-white, and almost all are of a high standard. This book will be of great value to senior dermatological students and to general practitioners, and is to be commended.

JOHN T. INGRAM.

THROMBOEMBOLIC DISEASES

Die Thromboembolischen Erkrankungen. Edited by Professor Dr. Th. Naegeli, Doz. Dr. P. Matis, Professor Dr. R. Gross, Professor Dr. H. Runge, Professor Dr. H. Sachs. With an Introduction by Professor Dr. I. S. Wright. (Pp. 1,045+viii; illustrated. DM. 158.) Stuttgart: Friedrich-Karl Schattauer Verlag. 1961.

This comprehensive textbook on thromboembolic diseases by West German and Austrian authors is designed to give a readable account of the subject to the increasing number of physicians and surgeons concerned with the management of thromboembolic conditions. History, anatomy, physiology, and statistical methods are set out in the first section, which contains an admirably detailed account of the physiology of blood clotting by E. Deutsch (Vienna); a notable feature is the set of tables inserted in the cover of the book giving details of the chemical and physiological properties of the coagulation factors, together with their synonyms and appropriate references to the literature.

The second part deals with the general clinical management of anticoagulation, fibrinolytic treatment, and surgical procedures, with an outstanding contribution on anticoagulation by P. Matis (Tübingen) and a detailed description of laboratory techniques by F. K. Beller (Tübingen).

The final and longest chapter is devoted to specific thromboembolic diseases, including lung conditions, cardiac infarction, and surgical, gynaecological, and ophthalmic disorders. It cannot have been easy for the editor to define the exact scope of the book. Thus, coronary thrombosis is fully discussed on 137 pages, and obstruction of the carotid and vertebral arteries receives some notice, but atherosclerotic occlusion in other vascular territories is excluded. No place is found for pulseless disease or thrombangitis obliterans, yet there is an article of 24 pages which deals with "meteorotropy" or the influence of weather and sunspots on thromboembolic episodes.

For the benefit of the general reader there are numerous references to the world literature. The discriminating British reader is likely to be interested in exploring the differences between German and British teaching; among anticoagulant drugs, he will find details of a number of lesser known substances such as the heparinoids "thrombocid," "eleparon," "paritol," and others, and the rare earths of the neodymium type; of

interest also are the German views on the vasoprotective properties of vitamins, antihistamines, phenylbutazone, and horse-chestnut extracts. On the other hand, there are only a few passing references to long-term anticoagulation, which does not appear to be widely practised in Germany.

P. F. MEYER.

EUROPEAN PSYCHIATRY

Impressions of European Psychiatry. By Walter E. Barton, M.D., Malcolm J. Farrell, M.D., Frances T. Lenehan, R.N., and William F. McLaughlin, M.D. (Pp. 128+x. No price.) Washington: American Psychiatric Association. 1961.

In 1958, thanks to the generosity of the Commonwealth Fund, the Commonwealth of Massachusetts sent to Europe a survey team of three distinguished psychiatrists and one psychiatric nurse. The team visited forty-seven different psychiatric hospitals and other institutions in Great Britain, Belgium, Denmark, France, and Holland. The American Psychiatric Association has now published the team's report.

The account of the team's visit to Britain and to other Western European countries contains much of interest both in their observations and in their commentary. The short summaries of the cases of the eighteen patients dealt with during their visit to the Amsterdam Emergency Psychiatric Service, for example, provide a glimpse of the actual work of this Service which could not be obtained from a more general description of its activities. In addition, British psychiatrists will be interested in reading this volume to see themselves as others see them, and will forgive the occasional factual errors in the account—which are comparatively few—in view of the great extent of the tour undertaken in the short period of six weeks.

G. R. HARGREAVES.

MAKING OF A DOCTOR

A Doctor's Memoirs. By A. I. Willinsky. (Pp. 183+x. 28s.) Toronto: The Macmillan Company. 1960.

It was hearing Osler deliver his well-known address on "The Master Word in Medicine" which decided the author of this book to become a doctor. "There was no doubt in my mind as I listened to him. I would become a doctor and strive towards the ideal he set before us." In due course and after overcoming various difficulties he passed the qualifying examination, but then "it was bitter to find that because I was a Jew all doors were closed to me when I graduated." The rest of the book describes how all (or nearly all) difficulties were overcome and Dr. Willinsky became a successful surgeon attached to the Western Hospital, Toronto.

The story is told in a racy manner with many good and some rather surprising stories interspersed. Dr. Willinsky was a skilled advocate of local anaesthesia, and found that, with some patients, "music was like a drugless relaxant," so he sometimes put a record on the gramophone while he was operating; on one occasion at least the music acted as a depressant.

In reading this book one is surprised to find that racial factors were so prominent in Canada 50 years ago, but it must be confessed that some of the difficulties recorded in this book may have arisen partly from the ill-advised words or actions of a rather over-sensitive individual.

ZACHARY COPE.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Scientific Basis of Medicine: Annual Reviews 1961. By the British Postgraduate Medical Federation. (Pp. 342+vii; illustrated. 40s.) London: The Athlone Press, University of London. 1961.

The Evolution of Medical Practice in Britain. Edited by F. N. L. Poynter. (Pp. 168+vi. 25s.) London: Pitman Medical Publishing Co. Ltd. 1961.

Disease and Injury. Edited by Leopold Brahdy, M.D. (Pp. 482+xviii; illustrated. £5.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1961.

Manual of Clinical Bacteriology. By Alexander Kimler, Ph.D. (Pp. 201+xiii; illustrated. 38s.) Philadelphia and Montreal: J. B. Lippincott Company. London: Pitman Medical Publishing Co. Ltd. 1961.

Acta Neurologica et Psychiatrica Belgica. English edition. ***Disipal Colloquium held at Brussels, 26th November 1960.*** (Pp. 114. FB. 100.) Brussels: Acta Medica Belgica. 1961.

Famous Faces in Diabetes. Compiled by Cecil Striker, M.D. (Pp. 256+xi; illustrated. No price.) Boston, Massachusetts: G. K. Hall and Co. 1961.

The Child Guidance Clinic and Delinquency. Implications of the Ingleby Report for the Child Guidance Services. The Seventeenth Inter-Clinic Conference for Staffs of Child Guidance Clinics—14th and 15th April, 1961. (Pp. 47. 3s. 6d.) London: National Association for Mental Health. 1961.

Industrial Conflict and Unions. By William H. Knowles. Reprint No. 159. (Pp. 291–312. 20 cents.) Berkeley, California: Institute of Industrial Relations. 1961.

Mental Health in the United States. A Fifty-Year History. By Nina Ridenour, Ph.D. A Commonwealth Fund Book. (Pp. 146+xii. 28s.) Cambridge, Massachusetts: Harvard University Press. London: Oxford University Press. 1961.

A Course in Epidemiology. Edited by J. I. Elkin. Translated from the Russian by C. R. Pringle, Ph.D. (Pp. 518+vii; illustrated. 70s.) New York, Oxford, London, and Paris: Pergamon Press. 1961.

Vertebrate Biochemistry. In Preparation for Medicine. By M. W. Neil, Ph.D., F.R.I.C. (Pp. 360+xii; illustrated. 40s.) London: Pitman Medical Publishing Co. Ltd. 1961.

The Mentally Handicapped and Their Families. A Social Survey. Maudsley Monographs, Number Seven. By J. Tizard and Jacqueline C. Grad. (Pp. 146+x. 28s.) London, New York, and Toronto: Oxford University Press. 1961.

Progress in Medical Genetics. Volume I. Edited by Arthur G. Steinberg, Ph.D. (Pp. 341+viii; illustrated. $9.75.) New York and London: Grune and Stratton. 1961.

Orthopaedics for Nurses. Edited by M. C. Wilkinson, F.R.C.S., and G. R. Fisk, F.R.C.S. (Pp. 363; illustrated. 37s. 6d.) London: Faber and Faber. 1961.

The Chromosomes. By M. J. D. White. (Pp. 188+viii; illustrated. 15s.) London: Methuen and Co. Ltd. New York: John Wiley and Sons, Inc. 1961.

Guildhall Lectures, 1960. The Language of the Gene. By Professor George W. Beadle. ***Communicating with Caliban.*** By Professor H. J. Eysenck. ***The Human Receiving System.*** By Lord Adrian, O.M., F.R.S. (Pp. 105; illustrated. 4s. 6d.) Organized by the British Association for the Advancement of Science and sponsored by Granada TV Network. London: University of London Press, Ltd. 1961.

The Analysis of Therapeutic Groups. Maudsley Monographs, Number Eight. By F. Kräupl Taylor, M.D., D.P.M. (Pp. 122+vii. 25s.) London, New York, and Toronto: Oxford University Press. 1961.

Doctors, Patients and Health Insurance. The Organization and Financing of Medical Care. By Herman Miles Somers and Anne Ramsay Somers. (Pp. 576+xix. 54s.) Washington, D.C.: The Brookings Institution. London: Faber and Faber. 1961.

Aerospace Medicine. Edited by Major-General Harry G. Armstrong, U.S.A.F.(ret.). (Pp. 633+xiii; illustrated. 144s.) London: Baillière, Tindall and Cox, Ltd. 1961.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY AUGUST 12 1961

AIMS OF CRIMINOLOGY

Criminologists have a reputation for unjustified academic pretensions, and the newspaper publicity that attends all their activities helps to keep alive the suspicions of those working in quieter and better-established disciplines. Yet criminology has a genuine contribution to make to the behavioural sciences, though as a field of study rather than a science in its own right. The techniques for examining unlawful behaviour do not differ in principle from those used by biologists, sociologists, anthropologists, psychologists, psychiatrists, and psycho-analysts in their studies of human behaviour. But the peculiarities and complexities of criminal behaviour present unique problems in research technique and methodology, and solutions to these problems have a general interest for investigators in other fields. Furthermore, criminals provide case material of great interest to psychiatrists and psychologists, much of which would never be encountered in ordinary clinical work.

In criminology the concept of simultaneously operating social, psychological, and biological factors is more than an academic talking-point. Criminal acts can hardly ever be analysed or described satisfactorily in the conventional terms of one discipline alone. The either/or schools of thought are dying out. It is no longer supposed that slum dwelling or parental rejection or psychoneurosis or any other single factor provides an adequate explanation of more than a few exceptional cases. The search for primary causes has given way to investigations designed to explore interrelationships between different factors. This kind of approach calls for real co-operation between investigators of widely divergent outlook and training, and requires the use of statistical methods for evaluating several variables simultaneously.

Another mark of progress in criminology is the recognition nowadays of the very wide variety of deviant, aberrant, and nonconformist behaviour that has to be examined. For a long time the use of the omnibus category "criminal" for behaviour as different as drunken driving, company fraud, murder, or sexual perversion, and of terms like crime waves and crime trends, has obscured the complexity of the actual situation. The boy house-breaker and the middle-aged woman shoplifter, for example, have such different backgrounds and motivations that nothing is gained by considering them together as if they were examples of the same underlying disorder. Official statistics have to be interpreted with caution, for they are based on legal definitions which vary with time and place, and they do not profess to take into account the social setting or the psychological meaning of the act. Imponderables like local tradition, or public opinion, or the accessibility of the telephone may influence whether a crime is reported, whether a charge is brought, whether a particular kind of injury is classed as "grievous" or only "actual" bodily harm, or whether eight milk bottles taken from separate doorsteps on the same morning constitute eight thefts or one. The sexual voyeur and the potential burglar may both find themselves convicted for being "on enclosed premises," and consequently be classed as offenders against property.

Discriminating analysis of criminal statistics serves to contradict popular misconceptions, and to provide useful leads for further research, but on the whole this method cannot answer the more fundamental questions. Convictions for murder, for instance, remain fairly constant, while convictions for violence against the person increase disproportionately, but the reasons for the difference are anyone's guess. Again, sex murderers are rare, and nearly all murdered children have been killed by their parents, and many murder suspects kill themselves, but such observations, though they give important leads, suggest more problems than they solve. The majority of juvenile offenders are not subsequently convicted as adults, and many persistent adult offenders were never convicted as juveniles, but it remains a mystery why some people are late starters in crime. Even on simple matters of incidence, statistics of convictions provide no reliable indication in the absence of information about similar undetected or unreported behaviour. In some instances, such as pilfering from department stores and homosexual behaviour in private, information from other sources suggests that the number of convictions recorded is much lower than the actual incidence of the offending behaviour.

The problems criminologists have to tackle bear little resemblance to the immutable riddles of natural science. Criminology is an applied science, and its subject matter necessarily changes with the passing interests and concerns of particular communities and the immediate preoccupations of legislators. Discussions of racial minorities, gang warfare, gun fights, and dope peddling feature more prominently in American than British criminological literature. The

application of traffic regulations has created a whole range of previously unheard-of offences, has doubled the business of the courts, and has provided criminology with an almost virgin field for research. As essentially practical, fact-finding investigators, criminologists are often called upon for expert opinions on topical controversies, such as the abolition of capital punishment or the reintroduction of flogging. Here lies a danger. Criminology, like any other science, can only answer questions formulated on its own terms. On matters of factual observation, such as whether changes in the frequency of executions correlate with changes in the murder rate, criminology should, in principle, provide an answer. But the evidence available is all too often scanty and inconclusive. Such as it is, it quickly finds its way into the appropriate governmental reports. One of the main reasons for the lack of evidence is that methods of controlled experiment are not possible in this field. One cannot, for instance, arrange for prisoners to be flogged and not flogged in accordance with a table of random numbers for the sake of comparing results.

The medical man, and especially the psychiatrist, has an important part to play in criminological research. He is well equipped to call attention to the differences of temperament, physique, and mental health which make some individuals particularly susceptible to inimical social influences; and may guide his more arithmetically minded colleagues away from exclusive preoccupation with easily measurable factors, like housing and income, towards the more subtle and perplexing questions of emotional life. But the conventional repertory of diagnostic labels will no longer suffice. It has long been known that the worse the criminal, the more frequent his convictions, or the more serious or unusual his crimes, the higher is the incidence of psychosis, epilepsy, brain damage, psychoneurosis, mental deficiency, or any other diagnostic category one cares to name. The really interesting problems centre on the reasons why some epileptics are violent, some neurotics persistent thieves, and some psychotics potential murderers. In the Parliamentary debate[1] last week on crimes of violence, two speakers urged the courts to make more use of medical evidence, so that "the wicked go to prison and the sick go to hospital," as Mr. David James put it. It is encouraging that the Institute of Criminology, which was recently established in Cambridge, and cannot fail to exert a considerable influence on research in Great Britain, includes a psychiatrist and a psychologist among its research staff.

[1] *House of Commons Official Report*, Thursday, 3rd August, 1961.

PATHOLOGY OF PERNICIOUS ANAEMIA

For the practising physician Addisonian pernicious anaemia does not present serious problems in diagnosis or treatment. The picture of slowly developing anaemia with slight icterus, a sore tongue, and perhaps loss of vibration sense at the ankles, in a middle-aged patient, is familiar and calls for haematological investigation. If laboratory tests show a macrocytic normochromic anaemia together with increased segmentation of polymorph nuclei in the peripheral blood, active megaloblastic erythropoiesis with occasional giant metamyelocytes in the bone-marrow, and an absence of gastric hydrochloric acid even after maximal stimulation of the parietal cells in the augmented histamine test, then the diagnosis of pernicious anaemia may be taken as virtually established and treatment begun with parenteral injections of vitamin B_{12}. The ensuing reticulocytosis and return of the blood count to normal provide the final proof of the correctness of the diagnosis. Monthly injections of 250 μg. of vitamin B_{12} are usually adequate to maintain a normal haemoglobin level and enable the patient to live out an unshortened life span.

This is satisfactory enough from the clinical viewpoint; safe and effective treatment controls what was once a fatal disease. Nevertheless, there are still unanswered questions on how the disease develops, and much research has been devoted to their study. Professor L. J. Witts, in the Lumleian Lectures to the Royal College of Physicians of London, published in this and last week's issue of the *Journal*, traced the progress of these researches from the original hypothesis of Castle, put forward more than 30 years ago. This is that pernicious anaemia is due to the absence of an intrinsic factor in the gastric juice which normally reacts with an extrinsic factor in the diet to produce an essential haemopoietic principle. The story is a fascinating and complex one and has yielded rich information about non-Addisonian megaloblastic anaemias and gastro-intestinal functions. So far as pernicious anaemia is concerned, however, the picture remains incomplete. Castle's extrinsic factor is known to be vitamin B_{12}, which is essential for haemopoiesis. Intrinsic factor is still unidentified, though its site of production in man is established with fair certainty as the gastric-gland area in the body of the stomach. The factor appears to act as a carrier of vitamin B_{12} across the mucosal membranes. It may be regarded as an amboceptor with two combining groups, one linking with the vitamin and the other available to link with an acceptor in the cells of the ileum, where absorption takes place. What happens to intrinsic factor after absorption is unknown.

[1] *Brit. med. J.*, 1960, 2, 282.

While work has continued on the mechanism of absorption of vitamin B_{12} and the role of intrinsic factor, there has also been a resurgence of interest in hereditary aspects of pernicious anaemia.[1] Relatives of patients have been shown often to have defective secretion of intrinsic factor, and the geographical incidence of the disease suggests that there is a familial predisposition. The concept has therefore grown that pernicious anaemia is due primarily to the possession of a genetic abnormality which causes a slowly progressive degeneration of the gastric mucosa. The mucosal degeneration leads to loss of acid secretion before intrinsic factor becomes deficient, and indeed in most affected individuals it is supposed that the progressive defect never reaches a stage where loss of intrinsic factor is complete enough to impair the absorption of vitamin B_{12} and so cause anaemia to develop. This hypothesis would explain why familial examples of pernicious anaemia, though frequent enough, are not more common.

Current views on the aetiology and pathogenesis of pernicious anaemia may be summarized, then, as follows. An individual is born with a predisposition to the disease, probably associated with a gene of low penetrance whose effect may never reach levels of clinical significance. With or without accelerating factors of defective nutrition or psychological stress, the gene may however lead to progressive atrophy of the gastric mucosa, usually in the middle or later years of life, with consequent loss of acid secretion. Diminished production of intrinsic factor commonly follows, and this may eventually proceed to complete loss. The amboceptor action of intrinsic factor is now no longer available to assist the transport of dietary vitamin B_{12} across the intestinal mucosa, and when stores of the vitamin have been exhausted the loss of its essential coenzyme activity in nucleoprotein synthesis in red-cell precursors leads to megaloblastic anaemia. Other less well understood metabolic functions of vitamin B_{12} must be necessary to maintain normal integrity of the central nervous system, and when deficiency is severe the lesions of subacute combined degeneration of the cord begin to develop and the full clinical picture of pernicious anaemia emerges.

MASS RADIOGRAPHY IN SCOTLAND

The statistical evidence for the progress made in the campaign against tuberculosis in Scotland is impressive. Between 1951 and 1956 the death rate from respiratory tuberculosis fell from 37 per 100,000 to 14 per 100,000; the notification rate fell from 154 per 100,000 to 117 per 100,000 (equal to an average annual drop of 4.8%); and the proportion of children aged 13 reacting to tuberculin fell from 66% to 32%. The contribution made by mass radiography to this remarkable improvement was perhaps disappointing: out of all the active cases notified in 1955, only 15% were discovered by this means. There was evidence of a diminishing return, because those with easy access to the mass radiography units were repeatedly coming forward for examination, while the difficult problem of the reluctant volunteer was not being overcome. But the two-year mass-radiography campaign in Scotland in 1957 and 1958 has significantly altered the position. I. M. Macgregor[1] has presented a comprehensive account of 22 intensive community surveys conducted during these two years. The number of people *x*-rayed was 1,844,268—a response rate of 68% of those resident in the defined areas, and 43% of the entire population of Scotland. In this campaign 12,094 new cases of respiratory tuberculosis were found: of these 4,328 (2.35 per 1,000) were regarded as having active disease and 7,766 (4.26 per 1,000) were thought to require observation.

During the two years of the campaign the number of new notifications of active disease which would normally have been expected from the surveyed areas was 7,684. In actual fact the total number was 10,050. The difference—namely, 2,366—is regarded by Macgregor as the true gain in active cases. The proportion of active cases among the total "yield" varied between 13% and 89% in different places and with different readers. Possibly, therefore, the true gain in active cases would have been even higher than Macgregor's estimate if double independent reading had been practised, but this manœuvre was not practicable in a campaign in which speed was the overriding consideration. Even so, the overall result showed that these short but intense M.M.R. surveys led to the discovery of 40% of the total new active cases notified in the period, in contrast to the 15% discovered in the year 1955.

It remains to be seen what the long-term results of this campaign will be. The future notification rates, actual and expected, should be compared in the surveyed and non-surveyed areas. In the non-surveyed areas the actual and expected trends should in the next few years roughly coincide. In the surveyed areas we might reasonably expect the increased fall in notification rates to be maintained. If that does happen the success of the campaign of 1957–8 will have been amply confirmed. In this

[1] Macgregor, I. M., *The Two-year Mass Radiography Campaign in Scotland, 1957-1958*, 1961. H.M.S.O., Edinburgh. Price 7s. net.
[2] Cochrane, A. L., Cox, J. G., and Jarman, P. T., *Brit. med. J.*, 1952, **2**, 843.
[3] —— —— —— ibid., 1955, **1**, 371.
[4] Cochran, J. B., Clayson, C., and Fletcher, W. B., ibid., **2**, 185.
[5] —— —— —— ibid., 1959, **2**, 1.

connexion the only figures so far available are for Scotland as a whole. The average annual decline in the notification rate from 1951 to 1956 was 4.8%. If this trend had continued the notification rate for 1960 would have been 87 per 100,000. The actual figure was 67 per 100,000. This accelerating decline in notifications may have several causes, but it seems reasonable to assume that the mass radiography campaign was the chief one.

The campaign has operated in two ways. First, it has substantially reduced the pool of previously undetected infection by the discovery of active cases. Secondly, it has anticipated and prevented relapse into active disease in many of the large number of patients brought under observation. The immediate effect has been on the notification rate. There has as yet been no change in the rate of decline in the amount of tuberculous infection in children aged 13, for it has continued to drop at the same rate as for the past ten years and in 1959 was 20%. An accelerating fall in this rate in the next few years would again confirm the success of the campaign.

Whether such an enormous undertaking could, or even should, be repeated seems doubtful. In the future the examination of special groups and small community surveys will probably be the better line of attack. The *x*-raying of all hospital out-patients and the offering of radiological examination to all hospital visitors as well should lead to useful results, since these would form a substantial proportion of the population. Alternatively, community surveys backed by tactful but painstaking and persistent home visiting of the type developed by A. L. Cochrane, J. G. Cox, and F. T. Jarman[2 3] in South Wales, and by J. B. Cochran, C. Clayson, and W. B. Fletcher[4 5] in Dumfriesshire, while slower in operation and more expensive to carry out, have proved to be of great value. Also important are surveys of selected occupational groups in whom even one unsuspected infective case could do great damage—for example, hairdressers and workers in catering establishments. Whatever the future policy for mass radiography may be, the further results of the great Scottish campaign will be awaited with keen interest.

TENNIS ELBOW

It is surprising that nearly ninety years after it was first described so little should be known about the pathology of tennis elbow, a common condition affecting a superficial structure. The lesion probably consists of a minor tear, perhaps in an area of degeneration, near the origin of the extensor carpi radialis brevis, which gives rise to symptoms only when repeated attempts at repair have been spoiled by continual use. The initial damage may result from any activity, often unaccustomed, which entails repeated extension of the wrist; it is thus common in housewives, for example, when it may follow a sudden enthusiasm for home decorating, while for the man of the house such activities as hedge-clipping may be the precipitating factor. Sometimes there is a history of direct trauma, usually a sharp knock to the outer side of the elbow, but racket games such as tennis and squash are relatively infrequent causes.

The presenting symptom is pain in the region of the elbow and the extensor aspect of the forearm. When severe, it may radiate to the dorsum of the hand and even to the middle and ring fingers, but, in contradistinction to the pain associated with irritation of the seventh cervical nerve root, there is never a paraesthetic quality. Discomfort may be felt most on comparatively trivial activities such as sewing or shaving which involve gripping with a stabilized wrist, while such tasks as carrying a heavy bucket are painless because the wrist hangs freely suspended. The cardinal signs of tennis elbow are pain on resisted movement of the radial extensors of the wrist, and tenderness which is accurately localized to the site of the lesion, most commonly just distal to the site of origin of the common extensor tendon at the lateral epicondyle of the humerus. *X*-ray examination of the elbow joint is negative.

In attempting to assess the results of treatment, the natural history of the condition must be considered. Most cases undergo spontaneous resolution in due course, though symptoms may persist for up to twelve months. The symptoms may quickly resolve if, at their onset, the wrist can be completely rested, but effective splinting constitutes a considerable disability in itself, and few people seek their doctor's advice immediately for what they consider to be a minor strain which will soon disappear. The injection of locally acting steroid preparations into the site of the lesion has revolutionized the management of this condition, and with care a high proportion of cases will respond satisfactorily to one or two such injections. The failure rate for this form of treatment is stated by various authors to range from about 5 to 25%, but, even if complete remission does not occur for some considerable time, the improvement gained usually allows the patient to continue with his normal occupation or to play his favourite game without difficulty. In the resistant case treatment by manipulation or by deep frictions may complete the cure. Persistent symptoms and signs of a tennis elbow are sometimes associated with a lesion in the cervical spine, when effective treatment of the neck lesion may produce a dramatic disappearance of not only the symptoms but also the physical signs of tennis elbow. Tennis elbow is not often a feature of rheumatoid arthritis, in which extra-articular signs are common.

In the exceptional case of tennis elbow in which symptoms are persistent and incapacitating and conservative treatment has failed, surgical treatment may become necessary, though most surgeons are loth to operate near the elbow if it can be avoided. R. S. Garden[1] has recently described a useful advance which

[1] Garden, R. S., *J. Bone Jt Surg.*, 1961, 43B, 100.

avoids this necessity. On the assumption that contraction of the extensor carpi radialis brevis is the principal cause of the pain, he has carried out Z-lengthening of the tendon of this muscle above the level of its synovial sheath in the lower third of the forearm. Analysis of the late results in fifty patients treated in this way suggested that most obtained complete and lasting relief from symptoms, and furthermore that the operation did not cause any loss of power of dorsiflexion at the wrist or efficiency of grip. Economically this operation appears to have the great advantage that no restrictions need to be put on the patient's activities other than the avoidance of vigorous use of the arm during the first few post-operative days.

EXTERNAL CARDIAC MASSAGE

New discoveries usually pass through four periods—scepticism, enthusiasm, the discovery of limitations and complications, and finally a balanced assessment. In spite of the fact that external cardiac massage was described by W. B. Kouwenhoven and colleagues[1] at the Johns Hopkins University School of Medicine only a year or so ago, there have already been reports from other centres of its successful use in clinical emergencies.[2] The method, which consists in rhythmic manual compression of the lower sternum in the supine position, seems admirably suited to attempted resuscitation of a case of cardiac arrest in the medical wards, where the small chances of recovery are often not felt to justify cardiac massage through a thoracotomy wound. External cardiac massage has the great advantage that it requires no apparatus and that it can be applied immediately the patient is seen, wherever he happens to be. Indeed, it is even claimed that maintenance of an effective circulation is as efficient with external as with intrathoracic cardiac massage,[2] but this view would probably not be generally accepted at present. With the advent of the external cardiac defibrillator, ventricular fibrillation as well as cardiac standstill may now be treated without opening the chest, the defibrillating electrodes being applied direct to the unopened chest wall. External defibrillation, however, introduces new hazards, owing to the strength of the shock necessary, and it is probably best to rely on defibrillation of the exposed heart as soon as ventricular fibrillation has been diagnosed electrocardiographically in the course of external cardiac massage.

Now J. R. Baringer and his collaborators[2] and R. R. Morgan[3] report complications that may result from external cardiac massage. Although at first sight a relatively benign manœuvre, it may none the less result in fractured ribs, haemothorax, haemopericardium, marrow emboli, and lacerations of the liver. Some of these complications were obviously trivial when viewed in relation to the seriousness of the emergency. In addition, complications became less frequent in Baringer's series as the hospital staff have become more familiar with the technique, special stress being laid on exerting pressure only on the sternum. On the other hand, lacerations of the liver, reported both by Baringer and by Morgan, with haemoperitoneum are a very grave hazard.

In view of these complications of external cardiac massage, the safest guiding principle for the present is that the technique should be performed only by those who have been carefully taught how to set about it and only after a doctor has confirmed the presence of cardiac arrest. If such precautions are not observed, enthusiastic laymen administering first aid might be tempted to perform external cardiac massage on someone who has merely fainted, with the possibility of producing serious injuries in an essentially healthy person.

[1] Kouwenhoven, W. B., Jude, J. R., and Knickerbocker, G. G., *J. Amer. med. Sci.*, 1960, **173**, 1064. See also *Brit. med. J.*, 1960, **2**, 1582.
[2] Baringer, J. R., Salzman, E. W., Jones, W. A., and Friedlich, A. L., *New Engl. J. Med.*, 1961, **265**, 62.
[3] Morgan, R. R., ibid., 1961, **265**, 82.

PLANT HUNTERS

The hunt for plants to supply medicinal substances is active to-day, as it has been since prehistoric times, though now it is doubtless more thoroughly organized. The pioneers who discovered how to obtain such drugs as opium, curare, and quinine have among their present-day successors the staff of the Tropical Products Institute, whose report for 1960 was issued last week.[1] This Institute, which comes under the Government's Department of Scientific and Industrial Research, reports that it has been considering the part it should play in the pharmacological assessment of plants from tropical territories, primarily those within the Commonwealth. "We believe that there may be potentially valuable new sources of drugs yet to be found which would be of economic benefit to the countries in which the plants are indigenous, and have noted the representations made by overseas governments to the Institute for technical assistance in this field. We have therefore recommended that the Institute should arrange, with assistance as appropriate from other organizations, for facilities to be provided for the pharmacological examination of plant materials."

In a routine screening programme 314 plants have been tested so far, and alkaloids found in some of them in sufficient quantity to merit further study. The initial work is carried out at Birmingham University in a testing unit financed by the Institute. It is hoped in this way to find plants that can be important cash crops in underdeveloped countries. Three yams from Zanzibar were examined to see whether they contained steroidal sapogenins which could be a starting-point for the manufacture of corticosteroids. Unfortunately these substances were absent. Though the name of groundnuts is apt to stir unhappy memories in some quarters, the Institute has studied current production in the African Commonwealth and Colonial territories and found that it is "more than sufficient to meet the need for supplementary protein of the most nutritionally vulnerable age group, i.e., that of 1–5 years." The

[1] *Report of the Tropical Products Institute, 1960*, H.M.S.O., 1961 (3s. net).

proteins in groundnuts, which are of particularly valuable quality, could do much to overcome the malnutrition prevalent in Africa owing to lack of that group of nutrients.

AMMONIUM CHLORIDE ACIDOSIS

When a healthy volunteer took 8 g. ammonium chloride daily for forty-four days,[1] acidosis developed during the first week, with a rise in plasma chloride, a fall in bicarbonate, and reduction in the *p*H of the blood. Excretion of sodium increased initially but soon returned to normal levels as more potassium was excreted to combine with the excess chloride. As might be expected, excretion of ammonia by the kidneys rose to very high levels, so that in the succeeding weeks of compensated acidosis less fixed base in the form of sodium and potassium was required and serum levels of bicarbonate and the *p*H of the blood tended to rise. There was also a slight increase in pulmonary ventilation, with a fall in pCO_2, and an increase in the amount of urine excreted. After the drug was stopped, a slight alkalosis developed, because renal excretion of ammonia returned only slowly to normal.

Ammonium chloride has been used therapeutically as a mild diuretic, as an acidifying agent, and as an expectorant. It also has a reputation for reducing weight and is occasionally given for this purpose. In the normal therapeutic dose of 4–6 g. daily the drug is harmless, but acidosis may develop in the elderly or in patients with poor renal function, and there is a danger of hepatic failure in patients with liver disease.[2] Recently two cases of severe poisoning have been recorded[3] in previously healthy adults who were in the habit of taking ammonium chloride for weight reduction. They were both young women who had impulsively consumed enormous amounts of the drug—in one case 82 g. in two days—in an effort to slim or with suicidal intent. The striking clinical features were mental confusion, hyperventilation, and vomiting. There was a profound hyperchloraemic acidosis, with depletion of body potassium, and a fall in blood *p*H and in pCO_2. Certain other interesting features were noted. Both patients had a leucocytosis, which is a well-recognized but unexplained accompaniment of acidotic states; one had transient hyperglycaemia and albuminuria; and the other, who was pregnant, developed tetany during recovery from the acidosis.

Sudden ingestion of 40–50 g. ammonium chloride by a healthy subject would be expected to prove fatal. As in other forms of metabolic acidosis, treatment with sodium bicarbonate or sodium lactate, given intravenously if necessary, will restore the electrolyte balance. Both of the present patients recovered after a total of 600–700 mEq of sodium bicarbonate had been given intravenously. During the recovery phase there is a fall in serum potassium, as in diabetic ketosis, and it is important to remember that the body stores of potassium may be low, so that supplements of it should be given by mouth to avoid hypokalaemia.

[1] Wood, F. J. Y., *Clin. Sci.*, 1955, **14**, 81.
[2] Sievers, M. L., and Vander, J. B., *J. Amer. med. Ass.*, 1956, **161**, 410.
[3] Reiman, A. S., Shelburne, P. F., and Talman, A., *New Engl. J. Med.*, 1961, **264**, 848.

DRUG COSTS AGAIN

Everyone concerned with the discovery, manufacture, prescribing, and dispensing of drugs must be getting a little tired of appearing in the dock on this charge or the other. Anyone would think that all the various groups of people responsible for the therapeutic triumphs of the modern era were a bunch of crooks. Those working in the pharmaceutical industry as well as those working in chemists' shops share one great disadvantage with their fellow creatures—they are human. It is as human to err in the conduct of a great and beneficent industry as it is to make mistakes in such an uncreative calling as the Civil Service. The politicians who misguide our destinies and yet try to administer the Health Service are just as likely to be wrong as to be right.

Some such thoughts as these must from time to time be harboured by those people who make it possible for the modern doctor to do his work, and for the modern patient to recover from diseases which killed his friends and relations a bare three decades ago.

The pharmaceutical industry has, like all those who criticize it, erred in a number of directions, all of which are now boringly familiar to the readers of mass-produced magazines. The medical press here and in the U.S.A. has been sharply critical of certain advertising gimmicks that were thought to do harm rather than good; and the industry's own trade association is strong enough to curb the indiscretion of its less responsible members. But now, as we read in the *Third Report* from the Committee of Public Accounts[1] (see *Supplement*, p. 121), once again there is to be a probing into the costs of advertising and the "considerable expenditure by manufacturers on sales promotion directed to general practitioners and hospital doctors."

With disarming naivety the committee goes on to say this: "It is admitted that doctors are influenced in their prescribing habits by persuasive representatives and elaborate literature, the cost of which must be reflected in the prices of the drugs." So they are going to prod the Ministry to give them full information on this "so that it will be possible to *judge* whether extravagant advertising costs are inflating the prices paid by the Health Service." (Our italics.) One must ask, who are they to judge, and how? The Minister of Health can add this to his list of artificial elements in the Health Service.[2]

The proprietors of medical journals—including the B.M.A.—would possibly benefit if advertising drugs was confined to medical periodicals. Plenty of doctors have written from time to time to complain about the spate of literature that goes through the letterbox. But we would humbly suggest to the Committee of Public Accounts and the Ministry of Health that the drug trade probably knows its own business best and will find it easier to continue to give its great benefits to the public and to the medical profession if its detractors cease to regard it as a darts board in a local pub.

[1] *Third Report from the Committee of Public Accounts*. Session 1960-61. London, H.M.S.O. Price 2s. net.
[2] The Elephant and the Whale, *Brit. med. J.*, 1961, **1**, 1479.

Clinicopathological Conference

DISEASES OF DIFFERENT SYSTEMS

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL

This patient suffered from diseases of many different systems, and it was of interest to attempt to assess the interrelationship and the relative importance of each in his final illness. The patient was treated at Hammersmith Hospital (Case No. 238,928; P.M. No. 9,267).

Clinical History

Dr. J. P. D. MOUNSEY: The patient, a Pakistani, was aged 64 years at the time of his death in 1960. He had come to this country from the North-West Frontier of India at the age of about 10 years. During the latter half of his life he had been a hospital cook, and at other times a hospital porter. He was first seen at the hospital in 1944, when he was complaining of dyspepsia, and a diagnosis of gastric ulcer was made. The ulcer was shown to be at the junction of the middle and lower third of the lesser curve in a barium-meal examination. He was treated medically and his symptoms improved, although from time to time over the subsequent years they recurred. In 1953 he had a second barium meal, but on this examination no ulcer was seen.

CHEST SYMPTOMS

Apart from the gastric ulcer and a right inguinal herniorrhaphy in 1954, he remained in relatively good health until the summer of 1955, when he was aged 58. Streaking of the sputum with blood now brought him to hospital. He said that he had had a cough for many years, both during winter and summer, with a cupful of mucopurulent sputum a day. His chest was wheezy at times and he had noticed variable dyspnoea on effort, but he could manage any distance on the level at his own pace.

On examination there was no cyanosis or clubbing and no enlarged glands. Chest expansion was found to be diminished and the breath sounds distant, with scattered rhonchi. His chest radiograph (Fig. 1) showed no evidence of tuberculosis or carcinoma. A diagnosis of chronic bronchitis and emphysema was made.

He attended hospital again in the winter of the same year, when wheezing and dyspnoea had become more troublesome. He was now lightly cyanosed, but apart from this the physical signs were unchanged. Culture of his sputum yielded a mixed growth of *Haemophilus influenzae, Streptococcus viridans,* and micrococci. He was recommended for long-term antibiotic therapy with penicillin V (120 mg. t.d.s.), but this was not maintained for long owing to difficulty in out-patient supervision.

AORTIC INCOMPETENCE

As a result of a radiograph of his chest taken to investigate a second small haemoptysis in 1957, it was noted that his left ventricle appeared enlarged and he was therefore recalled for a fuller clinical examination. Previous routine examination of his cardiovascular system in 1955 had shown moderate hypertension, 190/100 mm. Hg, with a loud aortic second sound, but no murmurs. An obvious early diastolic murmur was now heard and there was a wide pulse-pressure (210/95 mm. Hg). The electrocardiogram showed left ventricular preponderance. The development of aortic incompetence without evidence of associated stenosis, in a man of 61 years, in sinus rhythm, made it important to rule out syphilis, and in support of this diagnosis the blood Kahn reaction was found to be positive, although the blood Wassermann reaction and Price's protein precipitation reaction were negative. No previous history of venereal disease could be obtained, but it was thought that the results of the serological tests might have been partly affected by a course of penicillin injections which he received in 1952 for an infected finger.

COLLAPSED VERTEBRAE

He attended hospital three years later, in 1960, complaining of lumbar pain present for one month. This had come on gradually, and was worse on stooping and also in bed at night. A radiograph of his spine showed collapse of the body of L2 and also partial collapse of L3 (Fig. 2). Osteoporosis or secondary neoplasm were considered in the differential diagnosis. Examination of his cardiovascular system at the same time showed that his aortic incompetence had not increased. No convincing history of cardiac pain, fainting attacks, or of paroxysmal nocturnal dyspnoea could be obtained. He complained that breathlessness on effort was now very troublesome and had forced him to give up work two years previously, but this was largely due to his bronchitis.

In a more detailed radiological examination the diagnosis of luetic aortitis was further supported by the finding of calcification in the ascending aorta, a site where it is rare in simple atherosclerosis but common in syphilis (Fig. 3). Evidence of aortic aneurysm was also carefully looked for, but not found. Vascular calcification was also noted in the left anterior descending coronary artery and in the lumbar region of the aorta. There was, however, no clear evidence of calcification in the aortic valve.

It was felt that he required full investigation in hospital, and "veganin" (aspirin, phenacetin, and codeine) was prescribed meanwhile for relief of the pains in his back.

GASTRIC HAEMORRHAGE

A few weeks later a sudden gastric haemorrhage necessitated his admission to hospital as an emergency. He had noticed sudden dizziness, sweating, and shivering, followed by a liquid black stool. At the same time he became increasingly breathless and weak.

On examination, he was pale and thin and looked ill and older than his years. The tongue was furred but moist, the pulse small and rapid (100 a minute), and the blood-pressure had fallen to 70/40 mm. Hg. His temperature was normal. There was no local abdominal

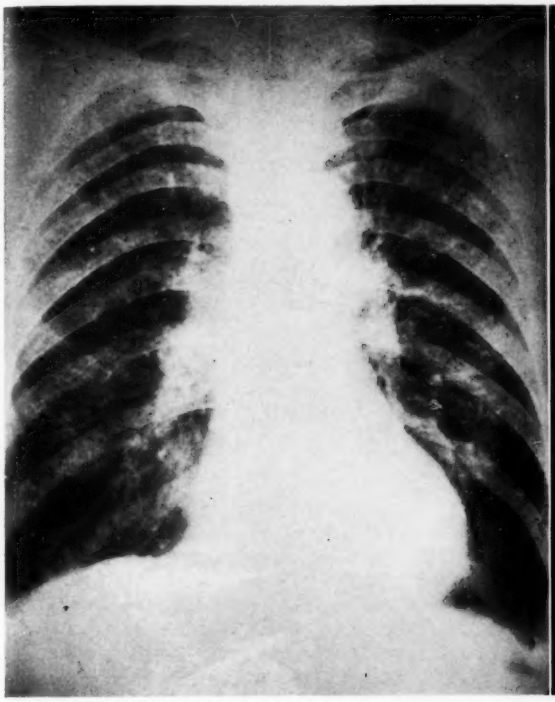


FIG. 1.—Antero-posterior chest radiograph. Streaky opacities especially at the right base. Heart normal size.

FIG. 2.—Radiograph of lumbar spine. Osteoporosis with collapse of the body of L2 and partial collapse of L3 vertebrae.

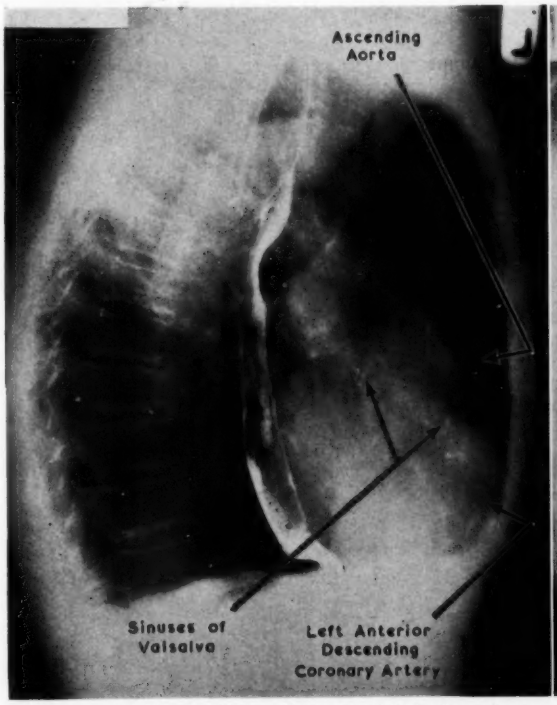


FIG. 3.—Right lateral chest radiograph. Calcification of the ascending aorta, of the sinuses of Valsalva, and of the left anterior descending coronary artery.

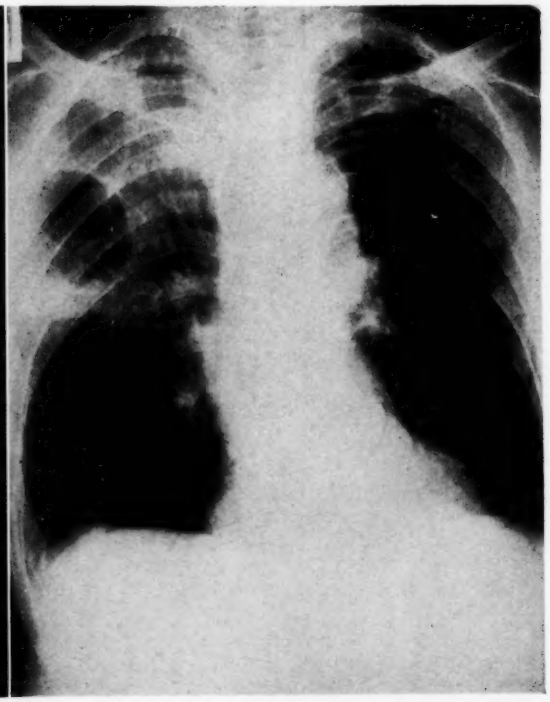


FIG. 4.—Antero-posterior chest radiograph. Thin-walled cavity in right upper lobe, with surrounding patchy consolidation and collapse.

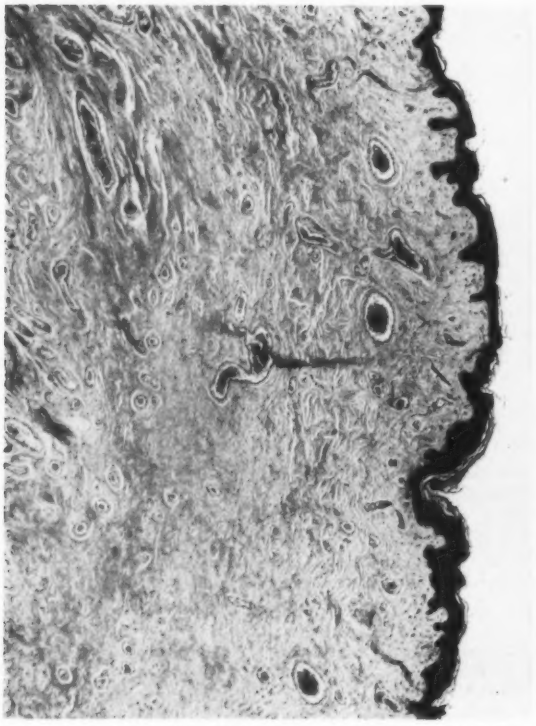


FIG. 5.—Glans penis showing scar of chancre. The deep bundles of collagen at the top of the picture are replaced by closely knit collagen of scar at the bottom. (H. and E. ×36.)

FIG. 6.—Aorta with fibrous scar of media. (Elastic/Gieson. ×58.)

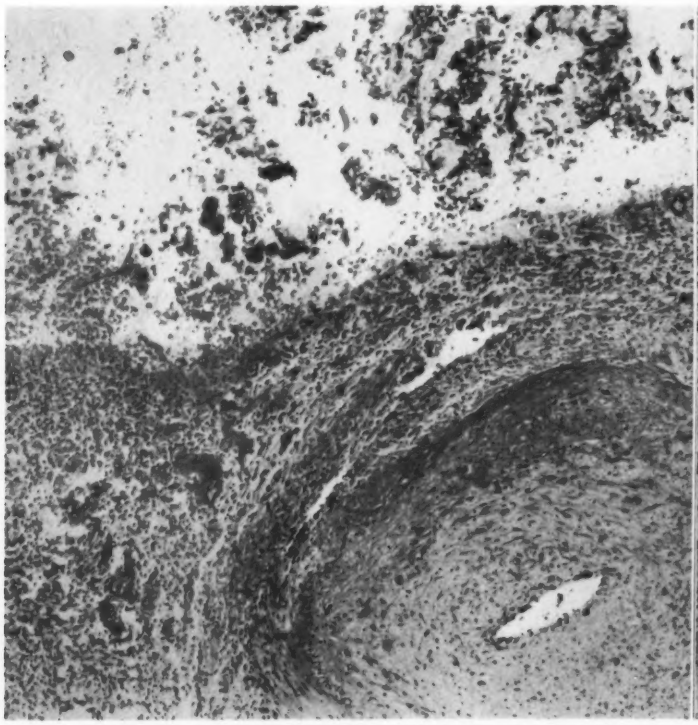


FIG. 7.—Gastric ulcer with large incompletely occluded artery in base. (H. and E. ×73.)

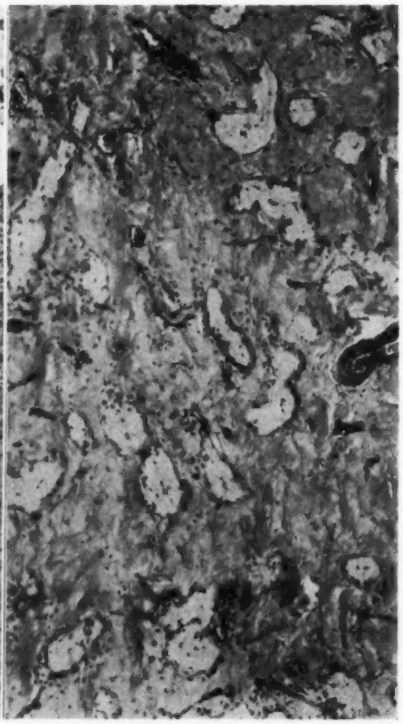


FIG. 8.—Testis showing shrunken hyalinized tubules separated by dense collagen. (H. and E. ×50.)

tenderness. He had a large, irreducible inguinal hernia. Rectal examination showed a melaena stool and prostatic enlargement that felt benign. In the cardiovascular system the collapsing pulse had been considerably modified by the sudden large loss of blood, but the long, loud, early diastolic murmur could still be easily heard. There were fairly loud rales and rhonchi all over the chest, and mucopurulent sputum. He was lightly cyanosed and his fingers were slightly clubbed. The chest was rather barrel-shaped, the accessory muscles of respiration were working, and expiration was prolonged. He was tender over his lumbar vertebrae on light percussion. No evidence of syphilis of the central nervous system was found. There was a scar on the glans penis, but his testes were of normal size and shape.

Investigations revealed a severe anaemia due to his sudden blood loss (Hb 8.2 g./100 ml.; P.C.V. 29%). Blood chemistry showed a high blood urea (127 mg./100 ml.) and low serum chloride (82 mEq/litre), with a slight diminution in serum albumin (3.5 g./100 ml.), changes that were all explicable on the basis of a large gastric haemorrhage. The rapid fall of the blood urea to normal levels (24 mg./100 ml.) in five days indicated that this was probably entirely due to absorption of blood proteins from the blood in the gut and not to associated renal failure. With the fall in blood urea the serum chloride rose to near normal levels. The blood cholesterol was normal. The blood calcium, phosphorus, and alkaline and acid phosphatase were all within normal limits. Sputum culture showed a mixed growth of *Haemophilus influenzae* and *Streptococcus viridans*. Radiographs of the spine revealed collapse of T 12 now, as well as of L 2 and 3.

MANAGEMENT

The bleeding gastric ulcer was treated conservatively, with blood transfusions and fluids by mouth. In all, ten pints (5.7 litres) of packed cells were given during the next 12 days to raise his haemoglobin eventually to 14.5 g./100 ml. By this time the patient's condition had greatly improved and it was possible to examine the stomach with "gastrografin"* meal, when quite a large ulcer was shown on the posterior wall of the stomach, without any evidence of neoplasm. On the strength of this finding and of the normal blood chemistry, it was felt that the collapsed vertebrae were probably due to osteoporosis rather than to neoplasm.

The patient was digitalized on admission and showed no signs of heart failure throughout his stay in hospital. A flare-up of his bronchitis on the second day was effectively controlled with a five-day course of tetracycline and sulphadimidine, with diminution in signs and sputum and resolution of pyrexia. However, on the twelfth day in hospital he developed pain in the right lower chest with increasing dyspnoea, followed after 36 hours by staining of the sputum. The temperature rose to 101° F. (38.3° C.) and there were generalized rhonchi and moist sounds, but no localizing signs in the lungs and no evidence of venous thrombosis in the leg. Radiographs of the chest revealed a large thin-walled cavity in the right upper lobe (Fig. 4). A diagnosis of pulmonary embolus, with later superadded infection, was made. A blood culture was taken which subsequently proved sterile, but no sputum culture was done. He was treated with oxygen, streptomycin (1 g. b.d.), and penicillin (1 mega unit 4-hourly). Anticoagulants were naturally avoided because of his ulcer. During the next 24 hours his progress was rapidly downhill, and he became cold, cyanosed, and hypotensive (B.P. 75/40). He was given mephentermine, hydrocortisone, 100 mg. intravenously, and cortisone, 150 mg. intramuscularly, and finally a noradrenaline drip was set up, but these measures had little effect and he died.

* "Gastrografin," a contrast medium for radiological investigation of the gastro-intestinal tract, is a 76% aqueous solution of the sodium-methyl-glucamine salt of N,N'-diacetyl-3,5-diamino-2,4,6-triiodobenzoic acid.

Clinical Diagnosis

(1) Bleeding gastric ulcer.
(2) Chronic bronchitis and emphysema.
(3) Luetic aortic incompetence.
(4) Osteoporosis of spine.
(5) Terminal pulmonary infarction, with superadded infection.
(6) Calcification of the left coronary artery.
(7) Prostatic enlargement.

Post-mortem Findings

Externally there was a large irreducible left inguinal hernia and the scar of a presumed healed chancre on the glans penis (Fig. 5).

The *heart* weighed 410 g. (normal 342 g.). Most of the increase in weight was due to hypertrophy of the left ventricle, whose wall measured 20 mm. in thickness (normal 15 mm.). The *right ventricle* was slightly hypertrophied to 4 mm. (normal 3 mm.). There was an old fibrous scar, 1 cm. across, in the posterior wall of the left ventricle near the apex. The chamber of the left ventricle was not enlarged. All valves were normal in circumference except the aortic, which was dilated to 95 mm. (normal 80 mm.). There was slight thickening of the edges of the cusps of the aortic valve in places, but mostly they remained delicately constructed. There was no commissural widening; the cusps were adherent for about 4 mm. There was a little calcification of the base of each coronary cusp, but most calcification lay just above the valve in the intima of the aorta, where a number of large hard plaques were conspicuous. The *coronary arteries* showed extensive calcification of the intima but mostly the lumina were widely patent. The diameter was reduced to about half the normal in the early part of the circumflex branch of the left coronary artery. Most of the arch of the *aorta* showed scattered calcified intimal plaques and an occasional stellate scar. In the thoracic portion of the descending aorta, plaques were small and flat and not calcified. In the abdominal portion, extensive, old, fibrous and calcified atheroma extended on into the common iliac arteries. Histologically (Fig. 6) the aorta showed occasional foci of destruction of elastic tissue in the media in the arch. There was no active syphilitic inflammation. The intimal thickening was complicated by considerable atheroma and one small mural thrombus was found. The appearances were of a healed, mild, syphilitic aortitis. The increase in the circumference of the aortic valve correlated with the clinical signs of aortic disease.

The *trachea* and *main bronchi* showed some mucosal congestion and contained frothy, clear mucus. There was no evidence of bronchiectasis, but histologically the main bronchi showed hyperplasia of the mucous glands,

and the walls of the small bronchi, especially in the lower lobes, were infiltrated by plasma cells and lymphocytes. Both *lungs* were overweight (left 740 g., normal 400 g.: right 900 g., normal 450 g.). They showed oedema and patches of bronchopneumonia, but in the posterior segment of the right upper lobe was a wedge-shaped, black, necrotic, cavitated area. *Pseudomonas pyocyanea* was cultured from this area. A pulmonary embolus lay in the appropriate artery at the apex of this wedge, and the lesion probably represented an infected infarct. Several small emboli were found in other pulmonary arteries, without infarction. Both lungs showed centrilobular emphysema which extended into the lower lobes. Special preparations were not made, but there was no obvious evidence of diffuse (panacinar) emphysema. Both *pleural cavities* were almost obliterated by adhesions, especially heavy in the left. There was a purulent pleurisy over the right upper lobe.

The *oesophagus* was normal, but there was a chronic *gastric ulcer*, 1 cm. in diameter, on the posterior aspect of the lesser curvature, about 10 cm. from the pylorus. The *intestines* contained altered blood. Histologically (Fig. 7) the ulcer was active and had a thick fibrous base; a large artery in the floor, which was probably responsible for the intestinal bleeding, was incompletely occluded by intimal thickening.

The kidneys appeared normal, as did the *ureters*, *bladder*, and *prostate*. The *left testis* was small, but the cut surface showed dense white fibrous tissue. Histologically the left testis showed only an occasional group of hyalinized tubules. The *right testis*, however, showed hyalinization and shrinkage of all tubules and very dense yellow connective tissue between them (Fig. 8). These changes were probably the result of syphilitic orchitis.

The *adrenals*, *thyroid*, and *spleen* were normal. The *vertebrae* had extremely soft trabeculae, and T 12, L 2, and L 3 were collapsed. Sections confirmed osteoporosis and healing fractures. Undecalcified sections showed osteoid seams up to 12 μ thick occasionally (excluding osteomalacia). The *bone marrow* itself appeared normal. The central nervous system was not examined (permission refused).

Pathologist's Diagnosis

(1) Bronchopneumonia and infected pulmonary infarct.
(2) Haemorrhage from gastric ulcer.
(3) Syphilitic aortitis.
(4) Calcification of coronary arteries, and small healed cardiac infarct.
(5) Osteoporosis of spine.
(6) Centrilobular emphysema.

Discussion

Dr. MOUNSEY: I think it may be of interest, in a patient suffering from so many different diseases, to try to see in retrospect which of them was of the most importance to him, and what was the sequence which finally led to his death.

FATAL SEQUENCE

As I emphasized in the history, he really didn't get on too badly until he was about 59, in spite of all the things wrong with him. But I think what happened at the end was this: Probably the collapse of two vertebrae, due to his osteoporosis, was the initial incident which set off the train of events that led to death, because this was very incapacitating and he had to take analgesics for it—I don't know how much veganin he took, but probably quite a bit. This may have caused the flare-up of his old gastric ulcer and brought on the haemorrhage—this is only supposition, but it is quite possible. As a result he had to come into hospital because of the large haemoptysis and be treated with transfusions and rest in bed, which would predispose to thrombosis; on the other hand we don't know that he had thrombosis in the venous system anywhere, but probably he had, because he developed pulmonary emboli. He then picked up a pyocyanea infection, which is a common thing for these old, fragile people to pick up, particularly in hospital, and in that way he was carried off.

Turning to his other diseases, I very much doubt whether the luetic aortic incompetence really contributed to his end and he seemed to have got along with it pretty well up to the age of 60. Secondly, his grossly calcified coronary arteries were none the less widely patent. I know that there was an infarct which was at the back of the left ventricle and towards the back of the septum, but it was not a very large one. It was certainly very old in appearance and it is doubtful whether it was really giving symptoms. So his heart seems to have stood up to this double insult with relatively little trouble, although, of course, what would have happened had he lived on is another matter.

BURNT-OUT SYPHILIS

Professor J. MCMICHAEL: That is a very interesting analysis, which it would be difficult to refute. This patient had a burnt-out luetic lesion, although he had had no treatment so far as we are aware.

Dr. MOUNSEY: So far as we are aware, he did not.

Professor MCMICHAEL: In the old days it was recognized that syphilis could burn out. If one finds aortic incompetence of mild or moderate degree in an elderly person, even with positive serology, it is not always necessary to start dramatic treatment, because at this age it is seldom a progressive disease. I think, Professor Harrison, some adherence of the aortic cusps is recognized although it is not a characteristic feature of syphilitic aortic incompetence, is it?

Professor C. V. HARRISON: I think it is rather something we find not uncommonly in all sorts of aortas and it may happen to coincide with the presence of syphilis.

CAVITATED PULMONARY INFARCT

Professor MCMICHAEL: The pulmonary infarct apparently became infected, and there was a necrotic bit of lung—isn't this rather unusual for a pulmonary infarction? Mostly the lung tissue survives, the patient gets over it, and the lungs become properly aerated again.

Professor HARRISON: Yes, I think it may depend upon sizes: this was a very big one. The ordinary ones we have seen with mitral disease are really quite small: this was a whacking great thing, and it is quite likely that the centre became necrotic. The other thing, of course, is, once you get organisms in a great thing like that, they in their turn may be responsible for the apparent necrosis.

Professor MCMICHAEL: Let us put it round another way: we see pulmonary infarctions so very commonly at necropsy—they must be counted by the hundred each year—yet the number which have become infected must be no more than one or two per cent.

Professor HARRISON: I believe so—very likely.

Dr. R. E. STEINER: We very rarely see cavitated infarcts now. When you said there was an infarct which had cavitated, I had my doubts. But, if the infarct breaks down and becomes infected, it is another matter.

Professor HARRISON: There is a snag that we all see, of course, in that *Ps. pyocyanea* has the very peculiar habit, which other organisms have not, of actually invading the vascular walls.

Dr. B. E. HEARD: I've looked carefully at the vessels of this lesion and I don't see any evidence of *Ps. pyocyanea*. I fancy that what happened here first was pulmonary embolism. He was debilitated, so there was more likelihood of necrosis, and he was a chronic bronchitic, so his organisms were there ready to invade the necrotic area.

Dr. M. D. MILNE: Could we not just ask in this respect what were the points that led to the correct diagnosis of the infarct? I would have diagnosed pulmonary abscess here and never thought of an infarction. I would have been wrong, but I want to know why I would have been wrong.

Dr. MOUNSEY: Well, we had very inadequate reasons. We didn't see the radiograph until a little later in the story. He complained of chest pain, he had haemoptysis, and he was an old man who had been in bed. The possibility of an infarct was the first thing that came into my head, and we were very surprised when we saw the radiograph with this abscess in it (Fig. 4). So we still stuck to our original diagnosis and added infection on top.

Dr. C. M. FLETCHER: I would like to take issue about not seeing cavitated infarcts. They are certainly uncommon, but one should think of an infarct even in an isolated cavitated lesion. We had a case with recent thrombophlebitis in which there were two small cavities which at first were thought to be tuberculous, but in the end we came to the conclusion they were certainly cavitated infarcts.

Dr. STEINER: But they were not infected infarcts which were breaking down and became cavitated.

Dr. FLETCHER: Well, he certainly had a little chronic bronchitis, but there was no gross infection at the time.

OSTEOPOROSIS AND DIET

Dr. GOODWIN: May I ask Dr. Mounsey a little more about the osteoporosis? This could be a very important factor in his analysis.

Dr. MILNE: Well, I think it is no use speaking too much on this subject. The classical theory of osteoporosis is that it is due to diminished formation of osteoid matrix, and that is the reason for giving steroid therapy, i.e., the mixture of oestrogens and androgens. I think later on this week we are going to have a very stimulating discussion of an alternative theory by Dr. B. E. C. Nordin, of Glasgow, that it is due to lack of calcium.

Dr. C. C. BOOTH: Could we take it just a little further? I think Dr. Nordin's view is that it is the lack of dietary calcium, isn't it? He suggests that these osteoporotics are losing calcium, and when he comes to take their dietary histories he finds that they have been getting less calcium than they should have in their diet. Do we know anything about the dietary history in this particular patient?

Dr. MOUNSEY: We don't know anything definite about his dietary history except that he was a man with a small appetite, so far as I know, and he looked a very poor specimen indeed. I should think there is ample room for suspicion that his diet excluded a number of important things, and that his dietary calcium was inadequate.

Professor MCMICHAEL: I should have thought his diet was likely to be adequate and varied as he was a cook.

Dr. MOUNSEY: A retired cook. He had been retired for three or four years because he was unable to hold a job because of his bronchitis.

Professor MCMICHAEL: Do you think this osteoporosis developed during the time when his diet might have been inadequate?

Dr. MOUNSEY: I think it could have. Of course he was 64 also.

Dr. FLETCHER: At a Clinicopathological Conference on a case of bronchiectasis,* the patient died of gross collapse of his thoracic vertebrae which caused such restriction of thoracic movement that he couldn't expectorate efficiently and really drowned in his sputum. Since then we have seen at least two other cases of chronic bronchitis with airways obstruction and osteoporosis in males, and now here is another one. Perhaps there is some association between these diseases.

Professor MCMICHAEL: It will be a syndrome shortly!

Dr. FLETCHER: Well, I don't think it is yet. Dr. Nordin, in the correspondence columns of the *B.M.J.* (1960, **1**, 277), after the previous case had been published, suggested that the osteoporosis might in some way be connected with respiratory acidosis. That was not possible in that case because there was no evidence of acidosis, and even in this case the plasma bicarbonate was only at the upper limits of normal, and it's unlikely that there was chronic carbon-dioxide retention.

"EMPHYSEMA"

May I comment on the diagnosis of emphysema here? The tendency to let the word "emphysema" slip in after "bronchitis" is regrettable. A "barrel chest" should not be described as supporting evidence. In any case the lateral radiograph, which we have got here (Fig. 3), doesn't look at all like a barrel. There was no radiological evidence of emphysema, except at the left base, where there was a suggestion that there might have been a little. None of the acceptable radiological signs of emphysema are seen in the radiograph except a very mild degree of flattening of the diaphragms. I would like to suggest that emphysema should be diagnosed on positive evidence and not on assumption. The correct diagnosis here is bronchitis with airways obstruction which was the cause of his dyspnoea.

Professor MCMICHAEL: Dr. Heard, I think you said he had centrilobular emphysema and you showed us convincing histological changes in certain areas. Of course, it is a matter of quantity, isn't it?

* "A Case of Bronchiectasis with Osteoporosis," *Brit. med. J.*, 1959, **2**, 1468.

Dr. HEARD: Yes, there is more than the ordinary quantity here, and, while centrilobular emphysema is usually confined to the upper lobes, here it extends down into the lower lobes. It is more extensive than the average member of the general population would be expected to have.

AMOUNT OF AORTIC INCOMPETENCE

Dr. J. P. SHILLINGFORD: There seems to be a considerable discrepancy between the physical findings of aortic incompetence and those found at necropsy. In 1960, you said, he had a long, loud, early diastolic murmur, and yet at necropsy the valve commissures were not widened and the cusps appeared normal.

Professor MCMICHAEL: I do not think the murmur, either in site or loudness, is diagnostic of the size of the leak. After all, the biggest pulse pressure documented was 210/95, so there never was evidence of what Thomas Lewis would call a "free" aortic leak with a gross collapsing pulse. He had, however, some left ventricular hypertrophy, but then he had a phase in which we would call him a hypertensive, with a pressure of 200—180/110.

Dr. SHILLINGFORD: Yes, indeed. In the final diagnosis should we call this syphilitic aortic incompetence or not?

Professor MCMICHAEL: I think he had a little bit, yes.

Dr. MOUNSEY: Don't you think that Dr. Heard's point is the relevant one here—I mean, we were rather worried that this aortic valve didn't show more than it did, but when one came to measure the circumference of the valve it was grossly abnormal. You have the figures on this, Dr. Heard.

Dr. HEARD: Yes, it was 95 mm., whereas the normal maximum is 80 mm.

Dr. MOUNSEY: Fifteen millimetres over normal. And, if one looks at this aorta, it's got this ring of calcium at the neck of the sinus of Valsalva and then the sinuses bulge out grossly underneath, and then below that is the ring of the aortic valve which is far too large, and so I imagine his incompetence was due to dilatation rather than aortic-cusp damage.

Professor MCMICHAEL: After all, this is a very common clinical situation in which we find, in a rheumatic heart, an obvious diastolic murmur, with no collapsing pulse. It does not affect a decision to deal with the mitral stenosis by surgery.

Dr. GOODWIN: I think that, if you have a very obvious collapsing pulse and a low diastolic pressure, you have severe incompetence. Apart from that, the intensity and length of the aortic diastolic murmur do give you some guide to the degree of aortic incompetence.

Professor MCMICHAEL: We never rely on a single feature for assessment. We take other things into account.

CALCIFICATION IN AORTA

Dr. STEINER: The sign of calcification in the ascending aorta in specific disease has been mentioned. I think we should discuss this further. I wonder how reliable this sign is. If there is excessive calcification, this may be accepted as syphilitic, but we often see calcification in simple atheroma.

Professor MCMICHAEL: Just above the valve.

Dr. STEINER: Yes, just above the valve, so I think one ought to be a little bit guarded.

Dr. J. W. LAWES: In a series of aortic calcifications examined radiologically, Elkeles[1] found that calcification in the ascending aorta, in the absence of very dense calcification in the descending aorta and elsewhere, was very suspicious of a syphilitic aortitis. He did find examples of quite dense calcification in the ascending aorta in simple atherosclerosis, however.

Dr. MOUNSEY: In 1945 Jackman and Lubert[2] looked at a series of patients with syphilitic aortitis proved at necropsy, and compared them with a similar series with severe atherosclerosis. They found that 22% of those with syphilitic aortitis had calcification of the ascending aorta, as compared with 3% of those with severe atherosclerosis. So it's not an absolute sign.

ULCERS AND ASPIRIN

Dr. BOOTH: I think Dr. Mounsey's assessment of this patient's troubles is probably quite correct. It is clear that he had a chronic gastric ulcer. It was shown radiologically in 1944 and Dr. Heard has shown the typical fibrosis of a chronic gastric ulcer. Now, studies at the Central Middlesex Hospital[3] show that, in patients coming into hospital with acute haematemesis or melaena, there is a higher incidence of a history of taking analgesics before the bleed than in patients with chronic ulcers continually attending out-patient clinics. This is the best evidence which has yet been put forward to suggest that aspirin, or veganin, which contains aspirin, may also cause a large bleed in a patient with a pre-existing chronic gastric or duodenal lesion. I would think, as Dr. Mounsey said, that this is what happened here. Two other small points: One usually underestimates the amount of blood lost in a patient who presents with an acute haematemesis. There is a very good paper on this by Tudhope[4] in which he shows that, if in a previously healthy person the haemoglobin is down to 80%, over half of the red-cell volume has been lost—much more than one usually imagines. As in this patient, you have to transfuse a good deal more blood than you at first think necessary.

ORIGIN OF BLEEDING

Finally, the question of early diagnosis. The idea is often pushed that you should try and make an accurate diagnosis of the origin of a bleed from the stomach or duodenum as soon as you can after admission. There are three ways in which this can be done: There's early gastroscopy, first; secondly, intubation of the stomach whilst the bleed's going on, the idea being that if you get no blood back and melaena is continuing it is a good assumption that bleeding is occurring from the duodenum—also the *p*H measurement may be helpful in determining whether it is a gastric or duodenal ulcer, for the *p*H is low in duodenal ulcer but may be above 3.0 in an acute gastric ulcer; finally, *x*-ray examination. I think that for general purposes an early gastrografin meal is the most valuable of these three methods. I would like to ask Dr. Steiner what he thinks about that.

[1] Elkeles, A., *Brit. J. Rad.*, 1958, **31**, 420.
[2] Jackman, J., and Lubert, M., *Amer. J. Roentgenol.*, 1945, **53**, 432.
[3] Alvarez, A. S., and Summerskill, W. H. J., *Lancet*, 1958, **2**. 920.
[4] Tudhope, G. R., *Quart. J. Med.*, 1958, **27**, 543.
[5] Fairbairn, A. S., and Reid, D. D., *Brit. J. prev. soc. Med.*, 1958, **12**, 94.

Dr. STEINER: Our experience is very limited here, and I must say we've been misled at times. After all, there may be a lot of blood clot in the stomach and it may be difficult to demonstrate a lesion. If positive, then *x*-ray examination is useful. But, if it's negative, it does not exclude a lesion. From the patient's point of view the examination is harmless and can be done in the ward. For instance, at the Central Middlesex Hospital the gastrografin meal is done on the wards, the patient is not screened, and only a few films are taken in different positions. They claim good results with this method.

Dr. FLETCHER: Doesn't aspirin disturb blood coagulation and increase the liability to bleeding?

Dr. STEINER: I don't think so, no. Professor Dacie?

Professor J. V. DACIE: I have no knowledge of this. I don't think so.

BRONCHITIS AND ULCER

Dr. FLETCHER: Just one other point about the gastric ulcer which was the immediate cause of death. Peptic ulcer is significantly associated with chronic bronchitis, as has been shown in epidemiological studies by Fairbairn and Reid[5] in the Post Office. They showed a significant association between sickness absence from bronchitis and from peptic ulcer. The association has also been shown in various clinical series. It is interesting that all the diseases which show a mortality gradient from rural to urban areas in this country are respiratory (bronchitis, carcinoma of the lung, tuberculosis), except for peptic ulcer. I suspect that this is because those who die from peptic ulcer tend to be those who, as in this case, have an associated severe respiratory disorder.

Professor MCMICHAEL: Well, that is one way of looking at it, but peptic ulcers often occur in people sick from almost any cause, and naturally you'll find them if you are looking at a lot of bronchitics. But people who have rheumatoid arthritis and elderly, ill, debilitated people often have peptic ulcers; peptic ulcers are awfully common in the advanced stages of illness of any sort in hospital. I would think you would have to have an enormous amount of control work to show that they were more significantly associated with bronchitis than with other debilitating illnesses.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report, and to the photographic department of the Postgraduate Medical School for the illustrations.

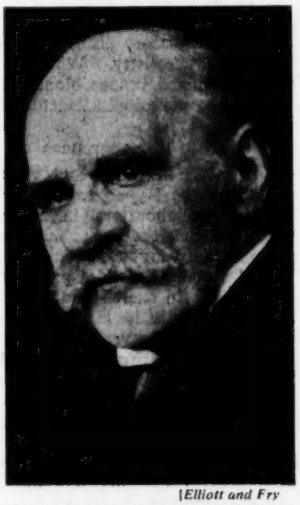
REGULATION OF RESPIRATION

J. S. HALDANE CENTENARY SYMPOSIUM AT OXFORD

[FROM A SPECIAL CORRESPONDENT]

John Scott Haldane was born in 1860, and, although the idea of celebrating the centenary of his birth was first discussed in Oxford in 1959, it proved impossible to hold this symposium before 1961. The delay of one year was, however, well worth while, as it enabled the organizers of the symposium, a special committee of the Physiological Society working under the leadership of Dr. D. J. C. CUNNINGHAM, to make certain, so far as was humanly possible, that the symposium should be representative and well prepared. The theme of the symposium was the regulation of respiration, primarily in man, which may be regarded as J. S. Haldane's main scientific interest, and it was held in the University Laboratory of Physiology at Oxford from July 24 to 27. Some sixty workers closely associated with this field of respiratory physiology were invited by the committee to attend the symposium, and another sixty or so physiologists attended by special application. The gathering included nearly every respiratory physiologist of world renown, and a good number of those, some indeed from the pre-1914 era, who had worked with Haldane.

The formal scientific proceedings of the symposium were divided into six main sessions, on Peripheral Receptors and Effectors, Central Receptors, Response to CO_2 and Interaction of Stimuli, Respiratory Adaptation to High Altitude, the Hyperpnoea of Exercise, and Miscellaneous Topics. Papers usually lasted for twenty minutes, and will be published together in a single volume (Blackwell Scientific Publications, Oxford) which should appear at the end of the year.



[Elliott and Fry

J. S. Haldane, C.H., M.D., F.R.S. 1860–1936.

Acclimatization to High Altitude

The papers of Drs. J. S. MILLEDGE and L. G. C. E. PUGH, "Acclimatization to High Altitude (6,000 metres) Extended over Several Months," was a fine example of clear-cut scientific work done under difficult conditions. By applying the techniques developed after the war in Oxford, under the original inspiration of Professor C. G. Douglas, Milledge and Pugh, working on the Ama Dablam glacier, were able to show that the main regulatory changes in acclimatization to altitude seem to be confined to the response to CO_2, the responses to hypoxia being largely unchanged after months of acclimatization. Only a part of the changed CO_2-response can be attributed to the acid-base changes in the blood. The need for a fuller investigation of the appropriate chemical factors, such as, for example, the acidity and bicarbonate content of the cerebrospinal fluid, was brought out both in this session and in that on Central Receptors, which made it clear that respiratory physiologists as a whole are still in grave doubt on when and where and how the various factors known to affect respiration make their impact on the organism. Dr. E. D. ROBIN tried to lead physiologists through the cell membrane to the mitochondrial membrane, and through that into the inner recesses of the cell, because, as he put it, following Mr. W. Suton, "that's where the money is," but the balance of opinion seemed to converge on the membrane of the appropriate cell in the C.N.S., and possibly on the concentration-ratios of various chemical species across that membrane, in accordance with the views of Professor H. H. LOESCHCKE, as the likely point for speculation and further experimental investigation.

Response to CO_2

There was at times during the symposium a feeling that some controversies were verbal rather than fundamental, and the session on Response to CO_2 and Interaction of Stimuli allowed Mr. B. B. LLOYD and Dr. D. J. C. CUNNINGHAM to put forward their quantitative exposition of the relationships between pulmonary ventilation, the alveolar gas pressures, and other factors such as temperature,

noradrenaline, and metabolic acidaemia. Their analysis, involving four separate parameters in the equation $\dot{V} = D(pCO_2 - B)(1 + A/(pO_2 - C))$ seemed to provide a sensible framework for assessing the effects of respiratory factors other than O_2 and CO_2, and worked well for their data on metabolic acidaemia, B being diminished in this condition, and for the data of Milledge and Pugh. This equation is merely an attempt to *describe* the respiratory relationships of normal subjects at elevated alveolar pCO_2's, but some such algebraic description is essential for comparison of ventilatory responses in one subject under different conditions or in different subjects. Nevertheless, it was clearly shown in a most important paper by Drs. A. CRAMPTON SMITH and J. M. K. SPALDING that the spontaneous ventilation of patients after artificial ventilation is affected by the previous ventilatory history and is not yet predictable from the blood chemistry. Whether subsequent work on the C.S.F. or mixed venous blood will explain away what now seem to be neurological factors remains to be seen.

Hyperpnoea of Exercise

The pCO_2 in the mixed venous blood figured in the session on the Hyperpnoea of Exercise. Dr. R. L. RILEY and his collaborators have made the most ingenious suggestion that the prime medium in which CO_2 exerts its effect on the ventilation is the mixed venous or pulmonary arterial blood. This idea pulls together the ventilation–CO_2 relationships in exercise and during CO_2-inhalation at rest, but the hypothesis lacks a proof of a receptor pathway by which the venous pCO_2 can make itself felt. The contributions to this session of Dr. F. F. KAO on cross-circulation experiments using three dogs, and of Professors M. NIELSEN and E. ASMUSSEN using cuffs on human subjects, both revealed no support for Riley's views but strongly implicated a neurogenic element in exercise ventilation. Dr. Riley's paper was, however, extremely stimulating, and a great many respiratory physiologists are no doubt at this very moment devising experiments to test his hypothesis.

The last afternoon of the symposium proper was devoted to special communications on original work on subjects related to Haldane's main research interests, including those outside the regulation of respiration, and one paper by Dr. G. SMITH on the treatment of carbon monoxide poisoning with oxygen at a pressure of two atmospheres was notable for the clarity with which it was presented and its very close relationship to Haldane's interest in applied physiology.

Historical Papers

This session was then followed by a scientific meeting of the Physiological Society. The first day of this meeting was devoted to historical papers appraising various aspects of the work of J. S. Haldane, including its life-saving applications to mining and diving. Professor C. G. DOUGLAS gave the introductory talk, having already given a most impressive paper earlier in the week on Haldane as a great man and a great scientist. Other outstanding papers in this historical session were those of Professor F. J. W. ROUGHTON on "The Chemistry of Respiration" and of Professor J. B. S. HALDANE on "A Possible Development of J. S. Haldane's Views on the Relation between Quantum Mechanics and Biology." Professor ROUGHTON, as always, was extremely clear, accurate, and stimulating, and anyone who hears him speak is grateful for the immense expertness he brings to this aspect of the work of J. S. Haldane. Professor J. B. S. HALDANE'S paper, though undoubtedly much harder to understand than Professor Roughton's, was also presented with clarity, insight, and a sense of adventure. It dealt with the notion that thought may be a quantal event, in the physicochemical sense, which takes a long time, perhaps a second, to be completed, and that this long duration is associated with a wide extension in the space in which the event may be said to be located, this space for a mental event being, according to Professor J. B. S. Haldane's calculations, about the size of the human brain.

Like Professor Douglas, Professor J. B. S. Haldane made two main contributions to the programme, his first talk having been based on work by himself and his wife, Dr. HELEN SPURWAY, on "The Regulation of Breathing in a Fish, *Anabas testudineus*." This was a model of work done under relatively primitive conditions with the simplest of apparatus, yielding quantitative and stimulating results.

The success of the symposium was shown by the very high attendance figures at all the sessions, and by the eagerness of the discussion in front of large numbers of people.

New Appliances

A PULSE GENERATOR

Wing Commander J. E. MALCOLM, honorary research assistant, Postgraduate Medical School of London, writes: In the construction of an analogue model of the heart and part of the vascular system, undertaken to develop a new theory of the action of the heart advanced by Malcolm,[1,2] it proved necessary to design a pulse generator. The latter is of interest in connexion with the pumping of blood, apart from the study of waves in this and in other fluids.

The requirements were as follows. The device had to be capable of exerting controlled suction as well as pressure for the formation of negative and positive waves. It was desirable that the fluid be confined to a simple system of tubing, not coming in contact with working parts, to facilitate sterilizing, should this be required, and to avoid discontinuities of flow. Transparent disposable plastic materials should be used, so far as is possible.

To give the waves a sharp leading edge considerable power was essential, and the controlling mechanism had to be capable of quick response—say, one cycle in a fifth of a second. A running-time of several hours was anticipated, but it did not follow that the machine would be functioning with a definite frequency: it might be necessary to generate waves analogous to those of a radar transmitter, where the pulse has a repetition rate, possibly variable, rather than a natural period. To bring this about, facilities to effect triggering and trigger-timing must be introduced.

A circulation pump driven by compressed air had been described by Röckemann[3] which possessed the requisite

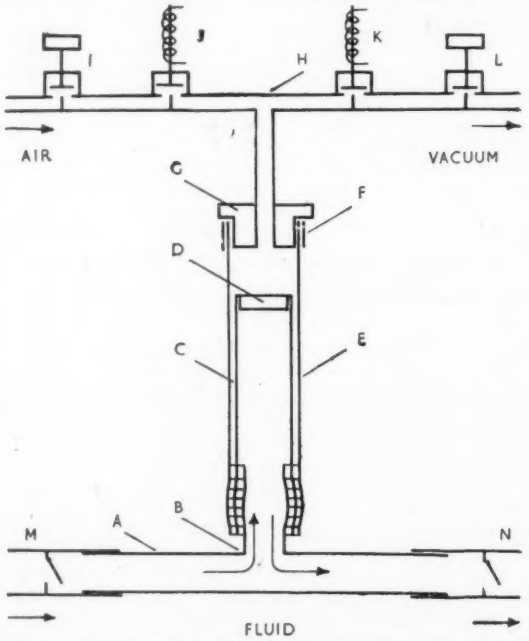


Diagram showing relationship of the component parts of the pulse generator.

power and rapidity of action. The control system, however, was not flexible enough for the project under consideration, and this led to the building of the apparatus described (see Diagram).

Fluid flowing within the rigid pipe (A) is free to pass through the junction (B) into the tube (C), the other end of which is closed by the plug (D). The tube (C), which may be made of "tygon," lies within the outer tube (E), made of "polythene," the sizes of the two tubes being such that they are a tight fit, the one upon the other, where the inner is stretched over a bulge in the rigid tube at the T junction. The other end of the outer tube (E) is securely fastened by a "jubilee" screw clip (F) to a flanged cylinder of "perspex" (G), through which passes one branch of the T tube (H).

Compressed air is admitted to the chamber formed by the tube (E) through a second branch of the tube (H), controlled by a manually operated screw valve (I) and also by an electrically operated solenoid gas valve (J). Air is evacuated from the chamber through the third branch of the tube (H), which is connected to a vacuum line controlled by an electrically operated solenoid gas valve (K) and a manually operated screw valve (L).

The solenoid valves (J) and (K) are connected to a power supply through a relay of the Post Office telephone type, the contacts being so arranged that as one solenoid valve is switched on the other is switched off. The relay, in turn, is driven by an electrically operated pendulum or other device which makes and breaks a single contact in the circuit actuating the relay.

In this manner the solenoid valves can be made to open and close alternately, so causing rise and fall of pressure in the chamber formed by the tube (E). The pressure change is transmitted to the fluid contained within the inner tube (C) and to that in the communicating tube (A), setting up wave motion. If one-way valves are inserted at (M) and (N) the apparatus may be used as a pump.

A twin-unit pulse generator has been designed to supply power to the "auricle" and "ventricle" of the analogue heart. It is self-contained, the vacuum being produced and compressed air supplied by two separate pumps driven by electric motors and mounted in the lower part of the cabinet. Each is connected to a cylinder which acts as a reservoir and effects "smoothing."

The solenoid gas valves, arranged in two pairs, are of the type known as "oil-dilution valves," employed in aircraft, operating at 12 volts (D.C.), supplied by a germanium bridge rectifier. In common with other commercially available valves of this nature, they are intended for lower frequencies than those of 1–2 c./s. at which they are employed here; overheating is prevented by connecting a resistance (10 ohms) in series and a condenser (1,000 μF, 25 volt working) in parallel with the power supply to each. When the current is switched on there is an initial higher voltage, which enables the solenoid valve to open: it remains open, although there is a subsequent voltage drop to 9 volts, until the current is cut off. The valve then closes.

For a "ventricular" stroke output of 20 ml. of saline, at 1 c./s., an air supply of 70 litres a minute is required. The working pressures are 0.7–1 kg./sq. cm. for compressed air and about 30 cm. column of mercury for vacuum. In the artificial circulation employed in conjunction with the analogue model of the heart, static pressures of 1.25 m. of water are readily maintained and pressures of more than 200 cm. of water may build up.

Acknowledgment is due to the Royal Air Force for supply of equipment; to the Postgraduate Medical School of London, in particular to Professor Ian Aird and Mr. W. J. Dempster, for research facilities in the experimental surgical unit; and to Dr. D. G. Melrose for the loan of apparatus.

REFERENCES

[1] Malcolm, J. E. (1960). *Nature (Lond.)*, **186**, 723.
[2] —— (1961). *J. Physiol. (Lond.)*, **157**, 2P.
[3] Röckemann, W. (1957–8). *Pflügers Arch. ges. Physiol.*, **266**, 671.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Cold Sprays

"Skefron" (Smith Kline and French).
"P.R. Spray" (Boots).

Composition.—Both of these preparations contain a mixture of fluorochloromethanes in an aerosol spray.

Pharmacology.—The boiling-point of these compounds is close to that of ethyl chloride (12.5° C.). When such liquids are vaporized the latent heat expended causes a fall in temperature. It would appear that both compounds exert their effects entirely by this mechanism. In all pharmacological respects they are inert. They differ, therefore, from ethyl chloride, which, with its toxic and general anaesthetic properties and flammability, must be used with special care.

Therapy.—Cooling sprays or compresses have been recommended from time to time for treating a variety of conditions associated with muscle spasm. This has usually been skeletal (lumbago, fibrositis, torticollis, etc.), but spasm of smooth muscle, such as in renal colic and dysmenorrhoea, is also said to have been improved. In addition, tension headache, migraine, post-herpetic neuralgia, and the pain from sprains appear to have benefited in some cases from cooling. The exact mechanism of pain relief is doubtful, but various possibilities exist: a substitution of cold for pain impulses to the brain; simple counterirritation; local vasoconstriction followed by rebound vasodilatation; or psychotherapeutic.

These preparations, which may be broadly classified with the older cooling remedies, are intended to be sprayed from a distance of 1–2 ft. for about five seconds. A second or third application may be given after intervals of half a minute. More prolonged spraying may be required in cases of severe pain. Not more than three to four treatments a day are recommended.

Side-effects.—Cold-burns may result from prolonged application. They are less likely to occur than with the usual ethyl chloride pack.

Contraindications.—Areas of broken skin or inflammation are best avoided. The nostrils, mouth, and eyes must be protected during applications to the head or face.

N.H.S. Basic Price.—5 fl. oz. container: "Skefron" 10s. 5d.; "P.R. Spray" 5s. 4½d.

The president of the British Medical Association, Sir DOUGLAS ROBB, recently unveiled at Rawene a memorial in the form of a sundial to Dr. GEORGE SMITH, the famous backblocks doctor of the Hokianga County, who died in 1958 aged 76. Dr. Smith anticipated the Welfare State in medical and hospital administration by many years, Sir Douglas told a large gathering of Dr. Smith's former patients, friends, and associates. An Edinburgh medical student of great promise and later holding a good practice in Scotland, he left to come to Rawene in 1914. In spite of the vast problems confronting him he identified himself at once with the needs of the district and undertook remarkable journeys by boat and on horseback in the service of his patients. In the social and medical fields, Dr. Smith instituted the over-all development of medical services in the district, trained nursing staff, devised a system of carrying sterilized surgical equipment, and trained his wife to give anaesthetics. He served both Maori and Pakeha tirelessly. "Who will forget his advice to the patient with peptic ulcer?" said Sir Douglas: "First go to your banker and tell him to go to hell."

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Abdominal Wound Dehiscence

SIR,—We think that Mr. H. A. Kidd (July 15, p. 173) has been mistaken in finding so simple an explanation for his cases of wound dehiscence as an inferior brand of catgut. Our own experience is at variance with his; and in one of our units the incidence of wound dehiscence during an 18-months period (October, 1959–April, 1961) was 1.8% (16 cases in 879 major laparotomies). In the majority of these there was an obvious cause (malignant cachexia, post-operative infection, post-gastrectomy pancreatitis, chest infection, paralytic ileus); in some, no doubt, the surgical technique also may not have been impeccable. Throughout this period we relied solely on Ethicon, and in no single instance could the wound disruption be attributed to the suture material.

We have no doubt that catgut as good as Ethicon is manufactured; it may even be that, as Mr. Kidd implies, London Hospital catgut is as good—or better—than Ethicon, but the important point is that if Ethicon is as poor as Mr. Kidd records—in which case many of us might wish to discontinue its use—we would like better evidence than that given by Mr. Kidd.

We naturally sympathize with Mr. Kidd in his own predicament. It is distressing to have to report an incidence of 12% of "burst" abdomens—and to find in the "black" months that even silk (presumably Ethicon's) is an unreliable friend. His deduction is a serious one, however, and those of us who know the care and precision with which Ethicon sutures are manufactured and the constant research that has gone to its perfection, and who appreciate the enterprise and the co-operation that have been so readily at the disposal of all surgeons, are unable to accept it on the basis of the information given in his letter.—We are, etc.,

Department of Clinical Surgery,
University of Edinburgh.

JOHN BRUCE.
WALTER MERCER.

SIR,—My recent experience would appear to support the contentions of Mr. H. A. Kidd (July 15, p. 173) about fraying and too early absorption of Ethicon catgut. It has so happened that in recent weeks I have had to re-open four abdomens. Brief particulars were as follows:

(1) Male, aged 75. Intestinal obstruction, bands, etc., July 2. Reopened for recurrent obstruction fourth day and intubated jejunostomy[1] performed. Catgut fragmented.

(2) Male, aged 46. Combined excision of rectum, July 1. Not well eighth day, burst abdomen eleventh day. Firm adhesion of small bowel to rectus sheath made it obvious that the deep layers of the wound had parted two or three days previously. Catgut fragmented and largely absorbed.

(3) Female, aged 41. Pyloroplasty, etc., July 4. Oedema of pylorus; reopened seventh day to pass Ryle's tube through pylorus. Catgut fragmented.

(4) Male, aged 52. Intestinal obstruction, carcinoma colon. Transverse colostomy, July 3. Paramedian incision reopened twelfth day and partial colectomy performed. Only traces of catgut found.

All wounds were uninfected, and Cases 2, 3, and 4 have healed without further incident. Case 1 developed a heavily infected wound (*Proteus*).—I am, etc.,

Lincoln. G. A. BAGOT WALTERS.

REFERENCE

[1] Luck, R. J., and Eastcott, H. H. G., *Brit. med. J.*, 1961, **1**, 1200.

Cooling of Operating Theatres

SIR,—I have read the account in *The Times* of July 11 of a patient who died of heatstroke after an operation in a theatre where the temperature was 86° F. (30° C.). I happen to work in the second oldest hospital in England, in which there has been installed a new ventilating system. This is temporarily sealed up with polythene whilst other rebuilding is going on. For this reason there is no proper ventilation, and the heat and humidity can rise to really unpleasant heights. To control this I use a very simple procedure. I have a large block of ice in a tin bath on to which is played the draught of an electric fan. This is a very simple and cheap expedient, and I find it far superior to a £12,000 installation in another theatre where I also work.

British hospital authorities install air-conditioning but appear frightened of the cost, so they frequently cut out the cooling to save expense. As we seldom have very hot summers in England it certainly seems more reasonable to use an inexpensive, easily procured method such as I have described.—I am, etc.,

Bristol. KENNETH H. PRIDIE.

Spontaneous Biliary Peritonitis

SIR,—The case of spontaneous biliary peritonitis recorded by Mr. E. F. Shanahan (July 15, p. 154) prompts me to report a very similar case I encountered recently. This was also a young woman, aged 25, who had complained of abdominal pain during 24 hours prior to admission.

At laparotomy about 1 litre of brownish-green, turbid biliary fluid was evacuated: the pancreas was swollen and some local spots of fat necrosis were seen. There was much oedema around the pancreas and the gall-bladder was noted to be tense and a little thickened. It contained no stones and there was no evidence of any perforation. I did not see any indication to open or remove the gall-bladder and simply closed up. Penicillin and streptomycin were given subsequently, but at no time did the temperature rise above 99° F. (37.2° C.) and her recovery was perfectly straightforward.

While acute pancreatitis is common enough, biliary peritonitis is unusual. These two cases show a clear association between the two conditions, and one must ask why biliary peritonitis is not more common. I would suggest that distension of the biliary system together with the continuing entry of pancreatic ferments into the bile duct is necessary to allow the permeation of bile into the peritoneal cavity. Peritoneal irritation might further account for some of the free fluid, which, in my case at least, was not normal clear bile.—I am, etc.,

Fermanagh County Hospital,
Enniskillen,
Northern Ireland. H. T. FLEMING.

Schizophrenia in General Hospitals

SIR,—The beliefs and impressions of Dr. Russell Barton (July 29, p. 307) with regard to the treatment of schizophrenia, while of undoubted interest, appear to us to be fundamentally misconceived. Schizophrenia is a condition which causes a very severe degree of distress and for which no definitive treatment is known. We therefore believe that no form of treatment, even if it offers only temporary relief, should be altogether discarded.

We note, with interest, his belief that deep insulin coma is not useful; we would prefer to agree with the considerable body of evidence which indicates that it produces remissions in the disease. We would, however, agree that it has been largely superseded by more effective therapies. With regard to E.C.T., this treatment is, in our view, of indispensable value, both in katatonic stupor and schizophrenia associated with a depressive affect, and there is also good evidence to show that it hastens remission when given in conjunction with phenothiazines in most other types of schizophrenia.

There is no doubt that, in a small number of cases, up to 5 mg. of trifluoperazine three times a day may be effective in controlling the disease, but in our experience up to three times this dose combined with an anti-Parkinsonian agent, such as orphenadrine or procyclidine, is more likely to be successful, and we have found that a combination of trifluoperazine and chlorpromazine given with an anti-Parkinsonian agent will often produce satisfactory results in more resistant cases. We are at the moment trying the effect of the monoamine-oxidase-inhibiting group of drugs, given together with phenothiazines, and have had some promising results, although we do not yet feel justified in expressing a definite evaluation of this therapy.

In view of these various possible psychopharmacological approaches to the treatment of this disease, we are astonished and dismayed that Dr. Russell Barton seems willing to limit his therapeutic effort to trifluoperazine in doses of up to 5 mg. three times a day.—We are, etc.,

M. S. BETHELL.
A. G. FULLERTON.
STELLA CONWAY.
R. H. BOARDMAN.

Herrison Hospital,
Dorchester.

Premalignant Disorders of the Vulva

SIR,—We have read with interest the paper by Professor T. N. A. Jeffcoate and Dr. A. S. Woodcock (July 15, p. 127) on premalignant conditions of the vulva, which, coming from a department whose fame is rightly world-wide, will attract the attention of all those interested in this difficult subject. It is the greater pity, therefore, that there is so much in this paper which calls for the sharpest criticism, and in the limited space of a letter only a few of its defects can be discussed.

We were first of all shocked by a variety of inaccurate statements. For example, they state, "Like skin cancer in general, involutionary changes associated with ageing are probably important predisposing factors" to cancer of the vulva. Whatever the relationship of age and involution may be to the development of vulval cancer (and it is interesting to note that one of the cases they describe was under 40), there is no evidence that age *per se* is an important factor in skin cancer in general. The authors exclude trauma as a possible factor in the causation of vulval cancer on the grounds that virgins and nulliparous women are affected. They disregard the commonest and most severe vulval skin trauma—namely, scratching. They also appear to acquiesce in the statement that condylomata acuminata are sometimes caused by chronic purulent discharges. These lesions are now widely recognized as being due to a virus infection, and, while they may possibly be encouraged by a purulent environment, they are not caused by it.

Some comment must be made on the illustrations and their legends.

Fig. 1.—This shows the changes of simple non-specific chronic dermatitis such as occurs on all parts of the body in many circumstances, and shows no features of leucoplakia. Even in the reproduced illustration it is apparent that the dermis is not in fact hyaline; fibrillary structure is clearly visible right up into the papillae, and the connective tissue is, if anything, more cellular than normal. The papillae and interpapillary epithelial ridges are clearly defined and regularly enlarged, and show only an exaggeration of their normal pattern.

Fig 2, labelled as atrophic leucoplakia, was "considered" [*sic*] to be a trichophytid reaction from fungus foot-infection. These histological appearances of epidermal flattening, hyperkeratosis, and subepidermal hyalinization must be unique for any *proven* trichophytid and are, of course, diagnostic of lichen sclerosus.

Figs. 3 and 4.—These show simple chronic dermatitis similar to Fig. 1, but in a more active state of inflammation. The "disorderly epithelial activity" with mitoses is no more than should be expected in an almost denuded squamous epithelium subjected to scratching and other inflammatory stimuli. This patient may well have had leucoplakia elsewhere on the vulva, and indeed it sounds from the history and subsequent events that she probably did, but the skin illustrated shows no signs of it. We cannot overemphasize the importance of what we have stressed in the past, that the atrophic or leucoplakic changes on the vulva are frequently accompanied, and may be almost obscured, by concomitant non-specific inflammatory changes of the kind illustrated here. Because the vulva from which this specimen was taken subsequently developed a cancer it does not follow that this was the type of lesion which predisposed it to neoplasia.

Fig. 5.—Whether this patient in fact had lichen sclerosus we cannot say, but certainly the piece of skin illustrated had not. It appears quite normal, there is no dermal hyalinization, no loss of papillary ridge pattern, no atrophy, a normal degree of surface corrugation, and normal keratinization.

Fig. 6.—On the right of the field the changes are of simple lichenification. It is possible that on the left there is a slight degree of hyalinization, and this may represent the margin of a leucoplakic zone, but the changes are very slight.

Of the five specimens illustrated none show the changes of leucoplakia. Three examples of non-specific inflammatory hyperplasias and one of lichen sclerosus are labelled leucoplakia, and a piece of normal skin is labelled lichen sclerosus.

In the face of all these inaccuracies and unproven assertions, and others to which we have not referred, many of the authors' observations and conclusions must surely be regarded with much misgiving. In particular, we regard as exceedingly dangerous their rejection of leucoplakia as a precancerous state, apparently on the grounds that exact definition is *sometimes* difficult. We deplore the suggestion made in this paper that all vulval diseases should be placed in a single blunderbuss category—"chronic epithelial dystrophy." Apart from its inherent definitive inaccuracy it is scarcely flattering

that this should be regarded as the highest peak of dermatological knowledge that can be attained by a gynaecologist. Much more important, however, such terminology would perpetuate and indeed worsen the existing obscurity. Because little is known about many skin disorders apart from characteristic clinical features and histological appearances, as in most other disorders in medicine, this is surely no reason for abandoning such knowledge as we possess when considering these disorders in the ano-genital region, particularly with regard to their natural history. We would once again make a plea for a continued intensive joint study of this problem by gynaecologists, dermatologists, and pathologists, a privilege that we have long been able to enjoy.—We are, etc.,

St. Thomas' Hospital, London S.E.1. H. J. WALLACE. I. W. WHIMSTER.

Fusion of Labia Minora

SIR,—I was interested in reading about Dr. C. J. Carr's description of a case of fusion of the labia minora (July 29, p. 314), because a similar case was recently admitted to the gynaecological department of this hospital.

The patient was a 53-year-old spinster who was admitted on July 27 of this year. She gave a history of difficulty in passing urine for the past two years, and a yellow offensive vaginal discharge for the past two months. She had previously had a subtotal hysterectomy at another hospital in 1937. There were, however, no details of the findings at this operation, since the records did not go back that far.

Subsequent exploration under anaesthesia revealed, likewise, an almost complete fusion of the labia minora, with a very small opening anteriorly common to both urethra and vagina. The labia were divided and a normal vagina and cervical stump were found. A bladder sound was also passed without difficulty. Later a cultural examination of the urine revealed a heavy growth of *Escherichia coli*, and a high vaginal swab-culture revealed a heavy growth of *Escherichia coli* and β-haemolytic streptococci of Lancefield's group C. Drug-sensitivity tests showed that these responded to sulphadimidine, and she was given a five-day course of this and then discharged home.

One therefore concludes that this was a case of cicatrizing stenosis of the labia minora secondary to infection.—I am, etc.,

West Middlesex Hospital, Isleworth. DAVID C. HUTFIELD.

SIR,—With reference to Dr. C. J. Carr's letter (July 29, p. 314) recording a case of fusion of the labia minora, I write to say that I have also come across a case of this condition in a hysterical woman. The condition appeared psychogenic in origin, and I attributed it to the influence of an unconscious desire on her part to avoid sexual intercourse by rendering this impossible.—I am, etc.,

Edinburgh 15. W. RONALD D. FAIRBAIRN.

Patients with Trophoblast Tumours Wanted

SIR,—We are writing to ask for assistance in a clinical test to determine the possible efficacy of 6-azauridine (AzUR) in the treatment of trophoblast tumours.

We have recently reported that AzUR given orally is an effective ovicide in the mouse,[1] terminating early pregnancy at dosage levels which produce no detectable toxic effect in the maternal organism. We have found that the first effect of the drug on the foetus is to reduce its rate of growth, and to produce a relatively structureless mole. Later, there is autolysis, beginning at the centre of the mole, rapidly progressing to the periphery, and eventually including the placenta. Within a few days of the onset of lysis, the products of conception are entirely resorbed and normal oestrus periodicity is resumed. Whilst we do not yet know the effect of AzUR on the human ovum, we do know that it is without toxic effect in human subjects in doses which, by analogy with the mouse, might be expected to be ovicidal. Thus, it has been given in doses of 300 mg. per kg. body weight daily for several weeks in leukaemia, without any of the adverse effects commonly produced by cytotoxic and cytostatic agents such as mercaptopurine and folic-acid antagonists.

Supplies of AzUR are limited by the difficulty of preparation. Moreover, we have found that different batches vary somewhat in activity, and there is no necessary relationship between their ovicidal activity and their toxicity. However, the Distillers Company (Biochemicals) Ltd. have undertaken to supply AzUR in amounts which, though limited, will be sufficient to determine its activity against trophoblast tumours. Each batch will be prepared in aqueous solution for intravenous use, and will then be tested in mice both for ovicidal activity and toxicity.

It is proposed that suitable batches of AzUR shall be available at the Highlands Hospital for use on patients under the care of Mr. David Savage. It is hoped that physicians and surgeons will refer cases of trophoblast tumours, especially chorion carcinoma, so that they may be considered for inclusion in the trial. The limit to the numbers will be determined by the amount of AzUR available, and it is hoped that this will become sufficient for the inclusion, later, of some cases of hydatiform mole. Inquiries concerning admission should be addressed to David Savage, F.R.C.S., Highlands Hospital, London N.21.—We are, etc.,

MARGARET A. SANDERS. B. P. WIESNER.
D. E. SAVAGE. JOHN YUDKIN.
Queen Elizabeth College, London W.8.

REFERENCE

[1] Sanders, M. A., Wiesner, B. P., and Yudkin, J., *Nature (Lond.)*, 1961, **189**, 1015.

Betamethasone

SIR,—The number of new corticosteroid preparations emerging from pharmaceutical research for the treatment of rheumatoid arthritis continues to increase, and it becomes more difficult to know which of these constitute a worth-while therapeutic advance. A regrettable consequence of the increasing pressure that is being placed on physicians to reduce the cost of their prescribing is that a bias may develop towards a preparation merely because it is of a known low cost. The only factor governing the choice of a steroid should be clinical merit, proved by a substantial number of hospital investigations. I now add my experience with betamethasone in the treatment of rheumatoid arthritis to those of Drs. J. H. Glyn and D. B. Fox (March 25, p. 876) and of Dr. D. S. Wilkinson (May 6, p. 1319) which have recently appeared in your journal.

From a group of over 500 patients under treatment for rheumatoid arthritis in a predominantly steroid clinic at the Dudley Road Hospital, Birmingham, 26 cases were selected at random from those who were stabilized on an oral maintenance dose of corticosteroid (prednisolone, triamcinolone, methylprednisolone, or dexamethasone). Betamethasone (" betnelan ") was substituted on a tablet-for-

tablet basis. A further 10 cases of rheumatoid arthritis, none of whom had previously received steroid treatment, were given betamethasone in amounts which, according to clinical requirements, varied between two and six tablets daily (one tablet contains 0.5 mg. betamethasone). During routine follow-up at fortnightly or monthly intervals progress was recorded and the dose was adjusted, as dictated by the patient's clinical condition and the incidence of side-effects. Analysis of the results after six months yielded these conclusions:

With regard to anti-inflammatory activity, betamethasone showed a poor anti-inflammatory corticosteroid effect, 12 out of 36 patients failing to respond satisfactorily. A degree of unpredictability of effect was reflected in the frequency with which it was found necessary to adjust the dose in previously stabilized individuals. If a simple tablet substitution is to be effective in those who respond, the strength of the present 0.5-mg. tablet should be increased (it is interesting to note that a similar observation was made by Hart[1] in relation to dexamethasone, which differs from betamethasone only by virtue of having the methyl group in the beta position). Side-effects occurred in 21 patients, a total incidence of 68% approximately. Although these were mild in some instances, they were sufficiently troublesome in 14 of the previously treated patients to warrant returning them to their former steroid. Moon-face developed in 10 cases, giddiness in four, and signs of gastric intolerance (nausea, flatulence, or indigestion) were complained of in three. With the exception of moon-face and flatulence, which had previously occurred in two and one patients respectively, while taking other steroids, the side-effects mentioned were new and were presumably due to betamethasone. Excessive weight gain, in four out of 36, was a particularly noticeable side-effect.

The incidence of side-effects occurring in my series is higher than that observed by the previous authors (although it might be pertinent to note that Dr. Wilkinson reported moon-face in six out of 11 patients who received betamethasone), and is very much in excess of the low incidence of these effects indicated by the manufacturers in their literature. The published work that has been carried out in this country with betamethasone is, as yet, very limited. It is my opinion that betamethasone is not as efficient a corticosteroid as some already in common use.—I am, etc.,

Dudley Road Hospital, Birmingham. R. O. GILLHESPY.

REFERENCE

[1] Hart, F. D., *Lancet*, 1959, **1**, 366.

Apnoea, Hypertension, and Conjunctival Oedema

SIR,—The case report described by Mr. E. C. Wood and Dr. T. A. Boliston (July 22, p. 217) invites comment. The syndrome of hypertension, flushed skin, raised C.S.F. pressure, apnoea, and unconsciousness is commonly seen where there is carbon-dioxide retention, and would seem to provide a possible explanation of these signs in this case. Perhaps there was some reason not specified in the text that had caused the authors not to consider this in the differential diagnosis. Regarding the conjunctival oedema, the presence of hypertension and vasodilatation would be sufficient to produce this sign, particularly if there was also a high mean intrathoracic pressure and the Trendelenburg position used.

I question the logic of the statement that "as the duration of the hypertension and conjunctival oedema corresponded to the period of respiratory apnoea the possibility that scoline caused these signs must be considered." It would seem unwise, in the absence of any other measurements, to even possibly incriminate only one factor in the aetiology of the hypertension and conjunctival oedema, since many physiological changes occur during the period of apnoea. Other factors would more adequately explain these signs than a toxic manifestation of suxamethonium. Furthermore, I cannot really agree that "the association of a low serum pseudocholinesterase with apnoea after the use of scoline supported the diagnosis of a scoline-induced apnoea." A prolonged apnoea following suxamethonium may be associated with a low pseudocholinesterase, but one can only hold suxamethonium responsible if a prolonged myoneural block can be demonstrated. No proof was given that in fact such a neuromuscular block existed. It is noted that supplementary doses of suxamethonium were given, presumably to control movement of the patient or adequately to control respiration, and during the operation it was necessary to give 5 mg. of D-tubocurarine because spontaneous respiration was detected, though the time of this injection is not given. In my experience, in cases of suxamethonium apnoea there is a most profound prolonged paralysis, and the duration of apnoea is closely related to the dose of suxamethonium. If supplementary doses of suxamethonium were required I doubt if this case was a true suxamethonium apnoea, and one must therefore seek a different explanation.

Whilst it is highly suggestive that this patient would be a candidate for a suxamethonium apnoea in that the pseudocholinesterase was extremely low and her sister had also had a prolonged apnoea following suxamethonium, it would be necessary to show that this patient had inherited atypical pseudocholinesterase. All cases of suxamethonium apnoea that I have investigated have inherited atypical pseudocholinesterase,[1] which Kalow[2] has shown does not metabolize suxamethonium in concentrations used clinically. I would therefore suggest that the term suxamethonium apnoea be reserved for those cases in which following suxamethonium a prolonged myoneural block can be demonstrated and atypical pseudocholinesterase is found in the serum.

Churchill-Davidson and Wise[3] have recently clarified the management of prolonged apnoea and stressed the importance of a rational approach. There can be little doubt that polypharmacy only obscures the diagnosis and may be harmful, and it would seem important to diagnose the cause of the apnoea before proceeding to therapy.—I am, etc.,

Alder Hey Children's Hospital, Liverpool 12. GORDON H. BUSH.

REFERENCES

[1] Bush, G. H., *Brit. J. Anaesth.* In press.
[2] Kalow, W., *Anesthesiology*, 1959, **20**, 505.
[3] Churchill-Davidson, H. C., and Wise, R. P., *Brit. J. Anaesth.*, 1960, **32**, 384.

Blood Transfusion for Mass Casualties

SIR,—Dr. R. A. Zeitlin (July 22, p. 242) refers to "the two common Caucasian blood groups O and A." Could he explain the significance of the word *Caucasian* in his phrase? — I am, etc.,

Birmingham. ROBERT J. HETHERINGTON.

*** Dr. Zeitlin writes: I used the term "Caucasian"—it should more correctly have been "Caucasoid"—to denote the ethnic group of Indo-Europeans, more commonly referred to as the "White" race, in contradistinction to the Negroid and Mongoloid races. The significance is that whereas in the Caucasoids the blood groups O and A occur in roughly equal proportions, and together constitute about 80% of the population, in the Negroids and Mongoloids the

frequency of group B rises steeply and often exceeds that of group A. The scheme for mass grouping (July 8, p. 93), using one (anti-A) serum only, would clearly be useless in a non-Caucasoid population.—ED., *B.M.J.*

Insertion of Intravenous Cannula

SIR,—We have tried most of the contemporary products intended to simplify intravenous infusion, but have found the disadvantage common to all is the large size of needle required to introduce a cannula of adequate diameter.

The method we now use has proved simple and effective—the cannula is introduced on the outside of the needle, the components being a long needle with stilette (we use a lumbar puncture needle), and a Pontex cut-down cannula. A needle is chosen which fits closely inside the cannula, the length of which is trimmed so that the point of the needle just protrudes. The end of the cannula is bevelled to correspond to the bevel of the needle. The procedure is exactly similar to the introduction of a Guest cannula.

No splinting is necessary—the arm can be moved fairly freely without danger of perforating the wall of the vein. There is no redundant needle to be strapped to the skin and the cannula never leaks, because it is larger than its hole of entry.—I am, etc.,

Llandough Hospital,
Penarth. C. K. JONES.

Vagotomy for Peptic Ulcer

SIR,—I was interested to read the letter by Mr. J. P. Lythgoe on this subject (July 22, p. 244). I am glad to read that he agrees that the electrical stimulation test "can detect very small nerves." Apparently in his work such small trunks were never missed. I am afraid that in my own hands, when I apply the test—having done what I consider a complete vagotomy—I find that it demonstrates incomplete nerve section in about 15% to 20% of cases. The nerves I have missed are usually very small—occasionally, in a patient with a thick oesophagus, somewhat larger. With the test these can always be located, found, and divided.

It might be interesting to know the results of post-operative insulin test meals in other series of patients where the electrical stimulation test has been used. However, there are good reasons why we should stop using this test completely. As Gillespie and Kay state (July 15, p. 175), "No one would deny that there are inevitable difficulties in comparing the results of gastric-secretion tests after a gastro-jejunal anastomosis with the results of similar tests before the operation." Also, there is this uncertain factor to which Mr. Lythgoe refers of "parasympathetic secretory fibres in splanchnic nerves." Let us be essentially practical and find the proved recurrence rate of vagotomy when done by competent surgeons without using the electrical stimulation test, and let us compare this with the recurrence rate when it is used.

The recurrence rate when the operation has been done without the electrical stimulation test—that is, without any test used at the time of operation—has been given by many workers. Walters[1] found 13% recurrence; Edwards[2] reports a recurrence rate of 13.3%; and in over 700 patients operated on in the University of Chicago and reported by Rigler[3] 10.6% recurred. Weinberg[4] (quoted by Herrington *et al.*) found a recurrence rate of 5% in 300 patients. Recently, in England, Austen and Edwards[5] have quoted a recurrence rate of 5% in their own cases. Weinberg, in a personal communication to me, has expressed the view that the recurrence rate is between 5% and 15%.

Most workers agree that the incomplete nerve-section rate is high in less experienced hands, and is not absent in experienced ones. Dragstedt has always believed that persistent or recurrent ulceration was almost invariably due to incomplete section (Dragstedt and Woodward[6]). Stempien and Weinberg[7] recorded 11 cases where further operation had been undertaken for recurrence. Only in one was no intact vagus trunk found—but of course it may have been there.

The figure that we are at present lacking, and which I hope soon to supply, is the recurrence rate when the electrical stimulation test has in every case shown that all nerve trunks are divided. If Dragstedt is right, will this be 0% if we exclude the rare cases where the ulcer is of hormonal origin? It may be, as Lythgoe states, that in some humans stimulation of the vagus does not produce gastric contraction. If this is so it has not been our experience, and such cases—if indeed they exist—must be so few as to be unimportant in this work.—I am, etc.,

London W.6. HAROLD BURGE.

REFERENCES

1 Walters, W., paper read before the Pan-American Medical Association Surgical Section, Mexico City, Mexico, May 2–11, 1960.
2 Edwards, L. W., Classen, K. L., and Sawyers, J. L., *Ann. Surg.*, 1960, **151**, 827.
3 Rigler, S. P., in *The Physiology and Treatment of Peptic Ulcer*, ed. J. G. Allen, 1959. University of Chicago Press, Chicago.
4 Weinberg, J. A., quoted by Herrington, J. L., jun., Edwards, W. H., and Edwards, L. W., *Surgery*, 1961, **49**, 540.
5 Austen, W. G., and Edwards, H. C., *Gut*, 1961, **2**, 158.
6 Dragstedt, L. R., and Woodward, E. R., *J. Amer. med. Ass.*, 1951, **145**, 795.
7 Stempien, S. J., and Weinberg, J. A., ibid., 1953, **152**, 1593.

Isoenzymes of Alkaline Phosphatase

SIR,—In the report of the recent international conference in London on the biochemistry of human cancer (June 17, p. 1752) considerations of space necessarily prevented a full account being given of our results on alkaline phosphatase isoenzymes which were described by one of us (D. M. C.).

We are studying alkaline phosphatases by determining their Michaelis constants and other enzyme parameters, using starch-gel electrophoresis to purify the enzymes from serum and tissue extracts. So far, we have been unable to distinguish different tissue phosphatases by their mobilities on starch gel or by the patterns of bands produced. Thus we cannot comment on the interesting observations reported by Mr. A. W. Hodson and Dr. A. L. Latner (July 22, p. 243), since our approach, although also involving the use of starch-gel electrophoresis, is based on different principles—i.e., characterization by enzyme constants rather than by the pattern of enzyme migration.—We are, etc.,

DIANA M. CAMPBELL.
D. W. MOSS.
Postgraduate Medical School of London,
London W.12.

Medical V.C.s

SIR,—Major-General R. E. Barnsley's letter about medical V.C.s (June 17, p. 1762) contained reference to Henry John Andrews, who had served in the Salvation Army for 30 years, most of them in India.

My father, happily very much alive, was a junior partner in the early days of Andrews's medical career. These two entirely unqualified boys, missioners in a small village in Travancore, did what they could to relieve local suffering and collected a considerable

following. Books were their only guide. Andrews read, I think it was, Treves's *Manual of Surgery* the night before an operation, and my father gave the anaesthetic. If the stories now told me of their arrangements for studying anatomy are correct it is a wonder they lasted as long as they did even in an Indian State as opposed to British India and even in 1896.

Andrews qualified in America. He had laid the foundation for the Catherine Booth Hospital in Nagercoil, moved to Anand, and started another great hospital, and finally repeated this in Moradabad. Fourteen years after his death I had the honour to follow him to Moradabad. Such was his ability and vivid personality that no man, European or Indian, who had known him could forbear to talk of him with affection and devotion. Now those yearly helped by institutions he founded must be numbered by the hundred thousand.—I am, etc.,

Llewellin Hospital,
Kitwe, Northern Rhodesia. E. E. BARNETT.

Over-attractive Capsules

SIR,—A representative from a pharmaceutical firm has just been to see me and left me several samples. Most of these are most attractive to look at, particularly those capsules containing multicoloured granules. Is it any wonder that children make a bee-line for them? Many patients, particularly insomniacs, keep one or two capsules on their bedside tables within easy reach of childish hands. Should not these preparations be made less like sweets and bitter to the taste, so that children will not be tempted either by their appearance or palatability?—I am, etc.,

Guildford, Surrey. DICK GLOVER.

Zip Fasteners on Trousers

SIR,—Correspondents on this subject don't seem to realize that by cutting the lower part of the zip with pliers or wire-cutters the two halves can be separated with ease. A local anaesthetic, however, may still be necessary to remove the parts embedded in the prepuce.—I am, etc.,

Epsom. O. G. WILDE.

*** A number of other correspondents have written to make the same or a similar suggestion.—ED., *B.M.J.*

Society for Cytologists

SIR,—The First International Congress on Cytology, sponsored by the International Academy of Gynaecological Cytology, will take place in Vienna from August 31 to September 2, 1961.

While exfoliative cytology has been fully recognized as a branch of medicine in Europe and America, there are only a few isolated centres in Great Britain where cytology (endocrine or cancer) is practised. We believe that the creation of a Society may be of value to practising cytologists as well as to those studying the subject. Would those interested please communicate with the undersigned.—We are, etc.,

Chelsea Hospital for Women,
Dovehouse Street,
London S.W.3. MOIRA MURRAY.
FREDA OSMOND-CLARKE.

Postgraduate Medical School,
Ducane Road,
London W.12. ERICA WACHTEL.

Royal Free Hospital,
Gray's Inn Road,
London W.C.2. MARY EGERTON.

Obituary

J. PRESTON MAXWELL, M.D., F.R.C.S., F.R.C.O.G.

Professor J. Preston Maxwell, emeritus professor of gynaecology and obstetrics in the Peking Union Medical College, died suddenly in his car near his home at Brinkley, Cambridgeshire, on July 25. He was 89 years of age.

John Preston Maxwell was born in Birmingham on December 5, 1871, the son of Dr. James L. Maxwell. Educated at University College School and University College, he went on to St. Bartholomew's Hospital for his clinical training. He had a distinguished career there, qualifying in 1896, taking the F.R.C.S. in 1897, and graduating M.B. (with scholarship and gold medal in obstetric medicine), B.S. (with first-class honours and gold medal) in 1898. After holding resident posts at St. Bartholomew's Hospital he went out to Fukien, South China, as a medical missionary for the English Presbyterian Church. An outstanding clinician, he was an obvious choice for the post of director of the department of obstetrics and gynaecology at the Union Medical College, Peking—a teaching school supported by the Rockefeller Foundation. There he became a leading figure in the medical life of China. He was president of the Chinese Society of Obstetrics and Gynaecology; and for his services to the Republic of China he was decorated with the Chinese Republic Army and Navy Medal. He was elected to the Fellowship of the Royal College of Obstetricians and Gynaecologists in 1929. His published work included papers on osteomalacia, filariasis, intestinal parasitism, and food deficiencies.

Professor Maxwell returned to England about twenty-three years ago and settled at Brinkley, near Newmarket, where he was elected to the staff of the Newmarket General Hospital as consultant obstetrician and gynaecologist. For some time before the second world war he was secretary of the medical subcommittee of the Lord Mayor's Fund for the Relief of Distress in China.

Professor GORDON KING writes from Perth, W. Australia: The news of the death of Professor J. Preston Maxwell will bring a sense of deep personal loss to his many friends in almost every part of the world. My own friendship with him began in 1927, when he invited me to join the staff of his department of obstetrics and gynaecology in the Peking Union Medical College, which had recently been reorganized by the Rockefeller Foundation. In Peking, Preston Maxwell exerted a lasting influence not only upon his colleagues but on the lives of innumerable Chinese students who were destined to form the nucleus of the medical teaching profession of their own land. He was a most gifted teacher, a superb operator, and a man beloved by patients and staff alike. His own important researches into osteomalacia formed a major contribution to that subject, and he also had the capacity of stimulating younger men and women to undertake original work, the results of which may be seen to-day in many medical schools not only in China but in many other parts of the world.

No appreciation of Preston Maxwell would be complete which failed to mention the very sincere faith in God which actuated the whole of his life and activities. His numberless acts of kindness and thoughtfulness were carried out unobtrusively and often anonymously. The hospitality of the Maxwell household had an old-world charm, as many visitors to his home in Peking or to his beautiful summer cottage at Peitaiho, will recollect. Even after he retired from China, over twenty years ago, he still maintained a very full life, and his friends of all nationalities, whether American or British or Chinese, all regarded a visit to his country home in Brinkley as an absolute "must" when they were in England. His wife, who predeceased him, was a most charming character, and a true helpmeet in every

sense of the word. She was a gifted artist, and over the years she painted a series of portraits of Chinese patients with rare and interesting lesions. It was typical of Preston Maxwell that one of his last acts was to send this collection to me as he thought they might be of interest to some of the medical students of to-day. The gift only arrived four days before the news of his passing and will remain as a constant reminder of a truly great man.

ELLI CASPARI, M.D.

The death occurred at Queen Mary's Hospital, Sidcup, on July 28 of Dr. Elli Caspari, who practised in Bexley and North Cray. She was 55.

Elli Caspari was born in Germany on December 31, 1905. After studying at the Universities of Berlin, Würzburg, and Freiburg, she graduated M.D. of Würzburg in 1933. An extremely promising professional career was abruptly terminated by the Nazi regime, for, being of Jewish descent, she was not allowed to practise medicine and was forced to scrub floors and do other menial tasks in a hospital in Berlin. Through a Jewish refugee organization she was able to come to England in 1938, but she was separated completely from other members of her family, some of whom went to Brazil, while others ended their lives in the extermination camps. She arrived in England completely penniless, and obtained employment as a domestic help, since her medical qualifications were not recognized at that time in England. Miss MacManus, then Matron of Guy's Hospital, enabled her to train as a nurse, but during the war she was placed on the temporary *Medical Register* and held resident appointments at the Royal National Ear, Nose and Throat Hospital, at Ashton-under-Lyme Hospital, and at Runwell Hospital. The General Medical Council then recognized her qualifications and in 1948, the year after she became a naturalized British citizen, she became assistant to Dr. C. W. Brook at Mottingham. Subsequently she commenced practising on her own account at Bexley and at North Cray. She was an extremely competent doctor, with a very extensive clinical knowledge.

J. C. SUMM, M.B., B.Ch.

Dr. J. C. Summ, who practised in Burton-on-Trent, died suddenly on July 21, aged 48.

Julius Cecil Summ was born on November 21, 1912. A native of Northern Ireland, he was educated at the Royal Belfast Academical Institution and at Queen's University, Belfast, where he graduated M.B., B.Ch. in 1936. After filling a series of house appointments in Belfast and Nottingham, he came to Church Gresley in South Derbyshire to join Drs. Camac and Robertson in partnership. On mobilization in 1939 he joined his Territorial unit, the 137th Field Ambulance, and proceeded with it to France, being later involved in the operations leading to the mass evacuation at Dunkirk. When the Mediterranean campaign opened he was posted to the 14th (Light) Field Ambulance of the 7th Armoured Division (Desert Rats). He served with this unit throughout its wanderings in North Africa, and, when the campaign finished, continued through the invasion of Europe and the Low Countries to the final actions in Germany. He became second-in-command, and for his services was appointed M.B.E. After demobilization in 1945 he returned to his practice.

E. M. R. F. writes: The sudden and totally unexpected death of Julius Cecil Summ has caused great distress and sorrow amongst his many friends not only in South Derbyshire but also further afield. "Summy," as he was affectionately known to all and sundry, was a very active practitioner who worked at considerable speed and pressure with little apparent fatigue. He was immensely popular with patients and colleagues alike, and his keen concern for all matters pertaining to general practice was reflected in his continual interest in the College of General Practitioners (of which he was a founder member), the local Division of the B.M.A. (of which he had been honorary secretary), and the local General Medical Practitioners Group. His appointments included those of local certifying factory surgeon, clinical assistant in dermatology at the General Hospital, Burton-on-Trent, and divisional surgeon of the St. John Ambulance Brigade. He maintained also intensive interest in various local activities, especially in the fields of Rotary International and Freemasonry, in each of which he had held high rank.

At all meetings, medical or lay, "Summy" displayed an acute shrewdness and grasp of facts and problems, and his comments, many of them pithy, were always to the point. He had a generous share of native Irish wit, which, with his happy nature, qualified him to be an excellent after-dinner speaker or chairman at the more hilarious ex-Service functions. His philosophy of life was simple and direct. A critical but most loyal friend and colleague, he was a "character" who will long be remembered in the district by colleagues and patients alike. The deepest sympathy is felt for his widow, daughter, and son.

A. B. FLETT, M.B., Ch.B.

Dr. A. B. Flett, who had practised in Edinburgh for nearly 60 years, died on July 15 at the age of 85.

Alfred Binney Flett was born on December 7, 1875, and graduated M.B., Ch.B. at the University of Edinburgh in 1902. He was in practice in Edinburgh for the whole of his professional life. In his young days he was renowned as a rugby footballer, and later he became a prominent figure in the medical life of Edinburgh. Among the appointments he held was that of medical officer to Fettes College.

Sir STANLEY DAVIDSON writes: With the death of Dr. A. B. Flett Edinburgh has lost one of her best-known and beloved medical practitioners and a great sportsman in every sense of the word: it is sad to think that he and his Dandy Dinmont in his brown vintage two-seater Rolls Royce will no more be seen by day and by night outside the houses of his many patients in all parts of the city. "A. B.," as he was affectionately known to his friends, was a magnificent rugger player. He not only captained probably the greatest fifteen Edinburgh University ever had, but he played for Scotland, and later was honoured by being elected president of the Scottish Rugby Union. He was also an expert fisherman and shot, and a connoisseur of paintings and antique furniture. Blessed with a splendid athletic figure and good health, he was able to continue in active medical practice until a few months before his death. He will be missed greatly for his wide experience and skill as a doctor, and for the many kindnesses which he showed to his patients and friends.

WALTER L. BIERRING, M.D., Hon.F.R.C.P.Ed. F.A.C.P.

Dr. W. L. Bierring, president of the American Medical Association in 1933–5, died in Des Moines, Iowa, on June 24 at the age of 92. He had a long and distinguished career as a physician, teacher, and state health commissioner, and his influence as a wise and experienced counsellor in medical affairs was nationwide.

Walter Lawrence Bierring graduated in medicine from the State University of Iowa in 1892, and thereafter he studied for a time in Vienna, Heidelberg, and the Pasteur Institute, Paris. Returning to Iowa, he became professor of medicine in his own university in 1903. Later he held the chair of medicine at Drake University. After being in consultant practice as a physician from 1913 to 1933, he held the appointment of health commissioner for the State of Iowa for the next 20 years, and up to the time of his death he was director of the Iowa Health Department's division of gerontology, heart, and chronic diseases. From 1912–60 he was secretary and treasurer of the Federation

of State Medical Boards, and he helped to form the American Board of Internal Medicine in 1936 and the American Board of Preventive Medicine and Public Health in 1947. An ex-president of the National Board of Medical Examiners, he was a Regent of the American College of Physicians from 1930 to 1939. The American Medical Association honoured him by the presentation of the Distinguished Service Award in 1956.

Dr. Bierring was a widower and is survived by his two daughters.

E. R. C. W. writes: With the death of Dr. Walter L. Bierring there comes to an end a long life devoted to the highest ideals of our profession, and American medicine loses a well-known and well-loved Grand Old Man. Catholic in his interests, Bierring made many contributions to medical developments in the United States. After post-graduate experience in Europe, he was appointed to a chair of internal medicine in his early twenties, and became one of the pioneers of medical teaching in the Middle Western States. His interest in medical education was life-long, and his last visit to Britain was to attend the First World Conference on Medical Education in London in 1953. The problems of medical registration engaged his interest at an early stage, and he played a leading part in the movement to bring order into the chaotic situation then existing in the United States. A fervent advocate of reciprocity, he inspired the setting up of the National Board of Medical Examiners in 1915, and after the first world war organized reciprocal arrangements between that Board and the Conjoint and Triple Qualification Boards in Britain. He was, characteristically, an enthusiastic member of the Alpha Omega Alpha Honor Medical Society, and editor of its journal, *The Pharos*, at the time of his death.

Of Danish descent, Walter Bierring seemed imbued with the friendly charm of his ancestral homeland. In his professional life he was the embodiment of the Hippocratic ideal, not least, as the writer has good reason to know, in his relationship with young colleagues, to whom he devoted time and trouble unstintedly. The loss of a leg in comparatively early life did not deter him in the least, though, by limiting his physical activity in the clinical field, it may have played a part in turning his thought towards the realm of medical statesmanship, both national and international, and this became his absorbing interest in later life. As an ambassador both of his country and of his profession he can have had few equals.

The "Nunc dimittis" of such a life calls not for sorrow but for thankfulness and pride. Those of us the world over who were privileged to know Walter Bierring as a friend will not mourn his death but rather, in gratitude, treasure the memory of his life.

A. D. SPERANSKY, M.D.

Professor A. D. Speransky, director of the Institute of Patho-physiology and Experimental Therapy, Moscow, and a member of the Academy of Sciences of the U.S.S.R., died recently at the age of 74.

Alexei Speransky devoted all his professional career to studying the part played by the nervous system in the development of pathological processes. In the preface to the English edition of his book, *A Basis for the Theory of Medicine* (1935, New York), he explained that an appraisal of the data he had collected in his researches led to conflict with many existing views. "By the force of circumstances, we were compelled to pass to a version of the conception of the basic processes of general physiology, from the point of view of the nervous component in their origin and history. As a result, a system came into being capable not only of unifying around a common centre all the diverse data provided by the pathology and clinic, but also of advancing those branches of science along a characteristic and as yet untrodden path." Speransky's research, as he describes in his book, led him to a method of treating "polyarthritis" (and some other disorders) by "spinal pumping"—that is, the withdrawal and replacement of 20 ml. of cerebrospinal fluid about twenty times in the course of an hour. He claimed good results with this form of therapy, which he regarded as a special form of nerve irritation. American workers also had some success with the method, but from a small trial carried out in London in 1948 no conclusive results emerged so far as the treatment of rheumatoid arthritis was concerned.[1]

Professor Speransky's other research work covered a wide field, and among many honours he received from the Soviet Government were a Stalin Prize and two Orders of Lenin.

J. J. HARPER NELSON, C.I.E., O.B.E., *M.C.* M.D., F.R.C.S.Ed., M.R.C.P.Ed.

The obituary of Colonel J. J. Harper Nelson was published in the *Journal* of April 8 (p. 1044).

Dr. J. N. J. PACHECO writes from Bangalore, India: It was with much regret that I read the obituary notice of the late Colonel J. J. Harper Nelson. It reminded me of an incident, probably little known, which was one of the most extraordinary if not miraculous escapes that occurred in the first world war. It was related to me by Colonel Harper Nelson himself. I first met him when he was a young subaltern in the I.M.S. when I had just joined the Army as an assistant surgeon, at Bangalore, just 50 years ago. A few years later I met him on board the hospital ship *Madras*, in which I was serving and he was a patient, being invalided from that hell-hole "Mespot," back to India. At the outbreak of the war he was being sent back to India from England along with hundreds of other Indian Army personnel. The P. & O. ship in which they sailed was attacked by a U-boat in the English Channel and sank in a few minutes. Owing to a heavy list to starboard, all the lifeboats on the port side were put out of action. There was pandemonium and hysteria when there were not enough boats to rescue the men. Harper Nelson was one of the last to abandon ship and was forced to jump into the sea. He jumped either too late or too near the ship. Suddenly he found he was being sucked down, and in fact as the ship sank he was sucked down into one of the huge funnels. As he went down struggling, there was an explosion as the boilers burst. The force of the explosion from below blew him right out again into the sea. He lay stunned, bruised, burnt, and covered with oil and soot. He managed to keep afloat and then put all his failing energy to try to swim to a lifeboat near-by. He at last reached it and hung on to the lifeline. One of the ship's officers tried to push him off with an oar, thinking he was a khalasi, as Nelson was black all over from oil and soot, and there was little room in the crowded boat. When Harper Nelson shouted out for help he was at last recognized and taken in. Was it coincidence, was it chance or fate, that came to his help in an impossible and extraordinary situation? I prefer to think it was the hand of Providence that mercifully extricated him from certain death.

Medico-Legal

THE McNAUGHTON RULES AND ADULTERY

[FROM OUR LEGAL CORRESPONDENT]

On June 14 Mr. Commissioner Latey, Q.C., held that insanity within the meaning of the McNaughton Rules is a defence to a charge of adultery. Such a defence has been upheld in respect of the matrimonial offence of cruelty, but this is believed to be the first occasion on which it has been successfully relied on in respect of adultery (*The Times*, June 13).

The wife of the marriage charged her husband, formerly a hospital porter at a mental hospital, with committing an act of adultery with the intervener, a patient in the hospital.

[1] Savage, O., *Brit. med. J.*, 1948, **1**, 496.

The husband admitted the charge, and had been convicted at assizes in respect of the act. On behalf of the intervener, the defence was put forward that she was not guilty of adultery in that at the time of the sexual intercourse she was suffering from a defect of the reason due to a disease of the mind (namely, schizophrenia), so that although she knew what she was doing she did not know that it was wrong. The Court accepted this defence and held that it brought the intervener within the second limit of the McNaughton Rules. Accordingly the intervener was found not guilty of adultery and was dismissed from the suit. The wife was granted a decree nisi on the ground that the husband had committed adultery with a woman against whom the charge was not proved.

If it had been the spouse rather than the lover who had successfully pleaded insanity, the marriage would have remained undissolved. However, either spouse may petition for divorce on the ground that the respondent is incurably of unsound mind and has been continuously under the care and treatment for at least five years immediately preceding the presentation of the petition. This is not by any means easy to prove, despite the recent extending of the definition of "care and treatment" by the Divorce (Insanity and Desertion) Aet, 1958, and despite the fairly wide definition of unsoundness of mind. In deciding whether a person is "of unsound mind" the test to be applied is whether by reason of his mental condition he is capable of managing himself and his affairs.

Medical Notes in Parliament

QUESTIONS IN THE COMMONS

Hospital Building Programme

Mr. K. ROBINSON (St. Pancras, North, Lab.) asked the Minister of Health on July 31 to what extent the hospital capital development programme already announced for the current financial year and for 1962–3 would be reduced in the light of recent decisions of the Chancellor of the Exchequer. Mr. S. SWINGLER (Newcastle-under-Lyme, Lab.) asked the Minister for a statement on the effect of the Government's new economy measures on the Health Service; and, in view of the annual loss of productive work through sickness, what steps he was taking to maintain the expansion of those parts of the Service which directly contribute to the nation's fitness to work.

Mr. ENOCH POWELL said that with economy and increasing efficiency he expected the development of the Health Service, including the hospital building programme, to be able to continue without exceeding the financial limits indicated by the Chancellor of the Exchequer.

Mr. ROBINSON: "This is a very equivocal reply." When the Minister announced the increased Health Service charges in February he rested his whole case on the expansion and development of the hospital service. Unless he could give a categorical assurance the plans already approved by him would not be affected, he had put a false prospectus before the House. Mr. POWELL: On the contrary, it remained true that without the measures carried through earlier in the year there would have been less finance available for the developing parts of the Health Service. He expected both the Service as a whole and the hospital building programme to be able to go forward within the financial limits that the Chancellor had announced.

Lord BALNIEL (Hertford, Con.): Does the Minister's statement mean that the allocations to individual hospital boards for 1962–3 will remain as already announced? Mr. POWELL: Yes.

Scottish Plans

Dr. J. DICKSON MABON (Greenock, Lab.) asked the Secretary of State for Scotland to what extent he expected the present hospital building programme and those plans announced for 1962–3 up to 1964–5 to be modified in the light of the Government's decision. Mr. J. S. MACLAY told him that the buildings now under construction would proceed, and he did not expect any projects due to start in 1962–3 would have to be postponed. Later years were still under consideration. He did not expect that the maternity hospital programme in Glasgow would be affected.

Religious Convictions of Hospital Staff

Mr. D. HOUGHTON (Sowerby, Lab.) asked to what extent medical treatment and advice to patients in hospital was governed by the religious convictions of nursing or other hospital staff. He was told by Mr. POWELL, "Not in practice at all."

Mr. HOUGHTON drew attention to the judgment of Mr. Justice Havers on July 14; when giving judgment* for the defendant, Mr. Lindsay Morgan Park, of Selly Oak Hospital, Birmingham, he said that among the reasons accepted as valid for not telling the patient of the risks of a sterilization operation in the ward was the presence of Roman Catholic nurses, who would not tolerate any action for a sterilization operation or advice on contraceptives. "What does the Minister make of his reply in view of those circumstances?" he asked. Mr. POWELL said he understood that the time for an appeal in this case had not elapsed, and therefore he must not comment.

Mr. R. W. SORENSEN (Leyton, Lab.) asked if the Minister was not aware that in certain gynaecological and maternity cases this problem arose. In those circumstances would he agree that a patient, or friends of the patient, should be able to ask for a doctor or other medical officer who was not involved in this religious difficulty? Mr. POWELL: "I am satisfied the advice or treatment received by patients in the hospital service is not limited or governed by the religious persuasion of individual employees in the Service." Mr. R. J. MELLISH (Bermondsey, Lab.) said that without some of the girls with those religious convictions half the hospitals would not be open at all.

Care For Attempted Suicides

Mr. ERIC FLETCHER (Islington, East, Lab.) asked the Minister of Health what steps he proposed to ensure that all cases of attempted suicide coming to the notice of any hospital or general practitioner obtained psychiatric or other suitable treatment. Mr. POWELL said he would shortly be asking hospitals, local health authorities, and general practitioners to do all they could to ensure that everyone coming to their notice as having attempted suicide received appropriate care and treatment.

Mr. FLETCHER observed that the Minister no doubt realized that with the passage of the Suicide Bill an entirely new situation had arisen in which it would be the sole responsibility of his department to look after these people. Mr. POWELL: Yes. Mr. K. ROBINSON asked him to take special care about hospitals, in view of the fact that in the past at least one London teaching hospital was in the habit of treating the physical symptoms of an attempted suicide and discharging the patient without even referring him to the psychiatric department of the hospital. Mr. POWELL: "That is a point on which I am placing particular emphasis in the circular which I intend to issue."

[The Suicide Act received the Royal Assent on August 3.]

Unsplinterable Glasses For Children

Sir BARNETT JANNER (Leicester, North-West, Lab.) asked the Minister of Health whether he was aware that lenses of children's spectacles provided through the Health Service were not splinter-proof, and that an extra charge of £1 8s. was made for such lenses; and whether he would take steps to remedy this position. Miss EDITH PITT, Parliamentary Secretary, stated that unsplinterable lenses were available without charge where clinically needed.

Sir BARNETT JANNER asked what the Parliamentary Secretary meant by that. Did she not appreciate that these

* See *Brit. med. J.*, July 22, p. 251.

glasses should be available for every child in the schools? Was it not essential that a child should be provided with these glasses in any circumstances? Why did she not arrange that this should be done? Miss PITT said that what she meant was that where hospital specialists said that the child needed unsplinterable glasses they could be provided under the Service. She was advised that in general it was not justifiable to provide unsplinterable glasses for all children. Sir BARNETT JANNER: "Does not the Minister realize that this type of glasses is essential for children? What on earth is she talking about?" Miss PITT said she was advised that it was not essential in all cases. Cases, for instance, of a spastic child liable to falls would come within the definition of those in which unsplinterable glass was provided through the hospital service.

Mr. K. ROBINSON asked if the Minister would look at this again. Every child was liable to falls. Was it not most important that damage to eyes resulting from such falls should be avoided, if it could be avoided, even if it involves the Health Service in a little extra cost? Miss PITT: If the practitioner considered it necessary he could so recommend.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Dr. R. T. Sims has been appointed a University Lecturer in the Department of Anatomy, and Dr. J. G. Cruickshank a University Lecturer in the Department of Pathology, both with tenure from April 1, 1962, for three years.

Dr. C. S. Treip has been appointed the University Senior Assistant Pathologist to Addenbrooke's Hospital, with tenure from July 1, 1961, for three years.

Miss Ann Young (Newnham College) has been appointed an Assistant in Research in the Department of Human Ecology, with tenure from July 1, 1961, for three years and three months.

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At the quarterly comitia of the College held on July 27, with the President, Sir Robert Platt, in the chair, it was announced that the Baly Medal for 1961 had been awarded to Sir John Eccles, F.R.A.C.P., F.R.S., for his work and researches in connexion with the central nervous system and particularly the basic problems of central excitation and inhibition.

The Murchison Scholarship, held this year in Edinburgh, has been awarded to Dr. George W. K. Donaldson, and the Gilbert Blane Medal for 1961 to Surgeon Lieutenant-Commander J. H. Sewart, R.N.

Sir Harold Himsworth, F.R.S., was appointed Harveian Orator and Professor G. M. Wilson Bradshaw Lecturer, both for the year 1962.

The following lecturers were also appointed: *For 1962*, Lumleian, Professor R. A. McCance, F.R.S.; Goulstonian, Dr. R. W. Gilliatt; Oliver-Sharpey, Professor J. V. Dacie; Bertram Louis Abrahams, Professor W. D. M. Paton, F.R.S.; Humphry Davy Rolleston, Professor C. E. Dent. *For 1963*, Croonian, Professor W. Melville Arnott; FitzPatrick, Dr. A. H. T. Robb-Smith; Watson Smith, Dr. I. B. Sneddon; Marc Daniels, Sir Austin Bradford Hill, F.R.S.

The following Fellows of the College were elected officers for the ensuing year: *Censors*, Dr. E. R. Boland, Dr. L. B. Cole, Professor E. F. Scowen, Dr. W. D. W. Brooks; *Treasurer*, Dr. R. R. Bomford; *Registrar*, Dr. Kenneth Robson; *Harveian Librarian*, Sir Charles Dodds, F.R.S.; *Assistant Registrar*, Dr. N. D. Compston.

Dr. Kenneth Robson was appointed College representative on the governing body of the British Postgraduate Medical Federation, and Dr. J. R. Ellis on the Medical Services Review Committee; and Dr. S. W. Davidson was reappointed College representative on the council of King's College, Newcastle upon Tyne, University of Durham.

The following, having satisfied the Censor's Board, were admitted Members of the College:

B. K. Adadevoh, M.B., C. F. Allenby, M.B., Barbara J. Boucher, M.B., I. A. D. Bouchier, M.D., D. R. Boyns, M.B., A. D. Dayan, M.B., T. A. Don Michael, M.B., D. C. Fluck, M.B., M. S. Gotsman, M.B., M. W. Greaves, M.B., C. D. Holdsworth, M.B., W. E. Ince, M.B., C. T. Jones, M.B., K. E. de S. Karunaratne, M.B., Guat Siew Lee, M.B., A. H. G. Love, M.B., P. McCormack, M.B., S. M. Malik, M.B., W. H. Marshall, M.B., D. H. Morgan, M.B., J. A. Morgan-Hughes, M.B., J. D. Parkes, M.B., E. S. Paykel, M.B., Wai-On Phoon, M.B., M. G. Sahadevan, M.B., M. E. Samols, M.B., J. L. Seymour, M.B., J. T. Silverstone, B.M., B. S. G. Singhal, M.D., J. E. Stark, M.B., S. O. Suite, M.B., A. R. Tanser, M.B., J. A. Thomson, M.B., T. Varagunam, M.B.

Licences to practise were conferred upon the following 134 candidates who had passed the final examination in medicine, surgery, and midwifery of the Conjoint Board and who had complied with the by-laws of the College:

R. W. Adams, F. I. Amponsah, B. D. Apthorp, Antonia F. Bagshawe, J. S. M. Beales, P. L. Beet, M. S. Bell, R. J. E. Bellars, N. S. Bilkhu, A. G. Boohene, A. P. Bray, A. C. Buck, I. R. Cameron, Penelope J. E. Cave, P. B. Christian, D. P. Clowes, B. P. Coghlan, N. K. Coni, B. J. Cooper, I. L. Craft, Ann G. Creighton, D. Cripps, A. J. Crompton, B. R. M. Crook, R. J. Cryer, J. S. Cunningham, P. Curtis, A. J. G. Davis, Elizabeth J. Deman, C. J. Dingle, G. K. Dixon, G. M. Eames, G. H. Forman, E. Freeman, C. M. T. Gleave, Monica C. Grant, D. J. P. Gray, B. Greenwood, D. L. Hall, H. F. Harper, C. T. Hart, J. E. Haselden, D. A. Hay, S. Haynes, C. P. Heanley, Daphne M. Herbert, Joan C. Higgins, J. B. M. Holroyd, E. M. Holt, B. R. Hopkinson, C. J. Hughes, J. M. Hughes, Elizabeth A. Hutchinson, N. O. Ikedionwu, M. M. Ilahi, D. R. James, N. E. Jensen, R. Johnson, J. H. Jones, A. G. Karseras, I. R. Kerr, J. J. Kimerling, E. P. Kirk, N. J. Knight, W. A. Knight, J. E. A. Knowles, H. H. M. Knox-Macaulay, M. B. Laing, S. F. Leete, Li. B. C. Lewis, D. E. Lieber, D. K. Lund, Constance H. P. Lynne-Davies, J. O. McFarlane, Carol H. Martin, Florence G. A. Martins, Doreen M. Miller, Janine M. Miller, S. T. Minto, J. H. Moran, W. B. Morris, Elspeth A. Morrison, D. Nelson, O. Ogundipe, A. A. Ogunsanya, H. M. Patel, D. W. Pierce, G. Pincherle, J. P. Pryor, C. A. Quick, B. J. Radford, D. E. Rees, P. H. Rees, A. B. Richards, D. J. Richards, R. Robertshaw, J. M. Robertson, R. Rodriguez-Arganaras, A. P. Rubin, W. G. S. Russell, C. R. Scott, J. A. D. Settle, J. J. Shenkman, Valerie A. Shorter, M. E. Silver, Jennifer E. J. Simmonds, Irene P. Skoyles, Eileen D. Smith, Sheila K. Smith, A. P. Staz, M. D. Steyn, Frieda E. Stockings, B. E. Stone, M. F. Sullivan, R. Tanner, M. A. Taylor, D. R. Thomas, Brenda M. Thompson, A. J. Todd, Sophie S. Turner, A. J. Tyack, G. E. R. Vaughan, D. A. Vissenga, R. C. Wales, C. D. Walker, Jillian M. Wandless, K. Watwood, J. R. Weatherill, M. A. H. Webb, A. G. Wilson, A. D. Wright, Mary E. Yemm, L. J. F. Youlten, I. Ziment.

Diplomas in Anaesthetics, in Child Health, in Pathology, in Psychological Medicine, and in Public Health were granted, jointly with the Royal College of Surgeons of England, to the successful candidates whose names were printed (July 29, p. 319) in the report of the meeting of the council of the Royal College of Surgeons of England.

Diplomas were granted, jointly with the Royal College of Surgeons of England, as follows:

DIPLOMA IN INDUSTRIAL HEALTH.—J. Aryanpour-Kashani, M. R. Burke, P. J. Burke, S. M. Clerk, D. D. Desai, C. T. Jones, A. A. El H. Massoud, R. M. Oliver, D. S. Ross D. J. Terry.

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—S. M. Ahmadizadeh, D. Al-Nawab, D. M. Anklesaria, J. S. Araj, J. N. G. Evans, R. Gathercole, D. G. Ghanekar, A. H. Jafferey, S. D. Kerawalla, N. H. Mahindrakar, Thein Maung, T. R. Murugendrappa, J. G. M. Noel, A. L. Penn, N. N. Roy, M. D. Shankara, K. C. Sil, S. D. Singh, D. P. Tembe, S. B. Lagoo, A. M. Vidal.

Vital Statistics

Poliomyelitis in 1961

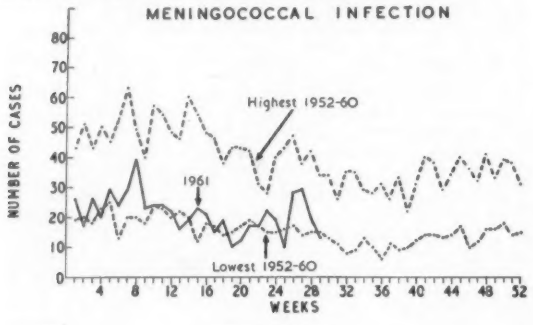
Up to the week ending July 29, 1961, there had been 346 cases of poliomyelitis notified in England and Wales: 247 of these were paralytic. Up to the same period the figures for the four previous years were as follows (paralytic cases in brackets): 1960, 289 (153); 1959, 783 (543); 1958, 832 (565); 1957, 2,106 (1,271). From the beginning of 1961 to July 22 three towns have had ten or more cases of poliomyelitis: Liverpool (32), Ipswich (24), and West Bromwich (13). During the week ending July 29 three further paralytic cases of poliomyelitis were notified in Liverpool.

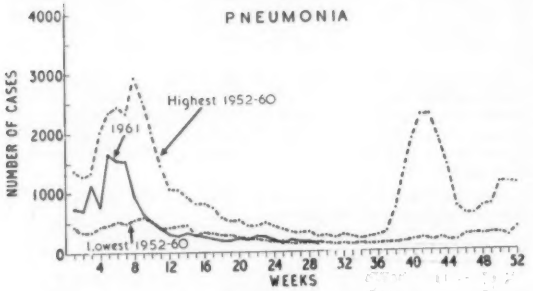
Illegitimate Births in the U.S.A.

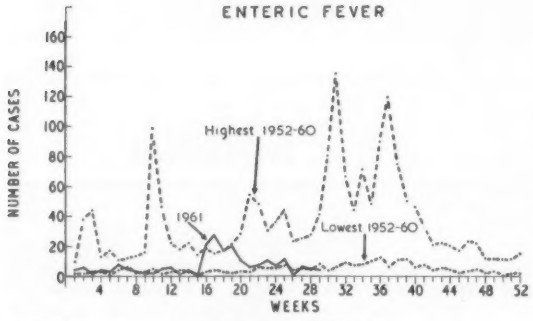
About 4,295,000 children were born in the U.S.A. in 1959, and of these 221,000 were illegitimate. The U.S. Public Health Service estimate that there were about 52 illegitimate births for every 1,000 live births in 1959. Among girls under 15 years of age there were 679 illegitimate births for every 1,000 live births; for girls of 15 to 17 the figure was 242; and for girls of 18–19 it was 106.—*New York Times*, July 29, 1961.

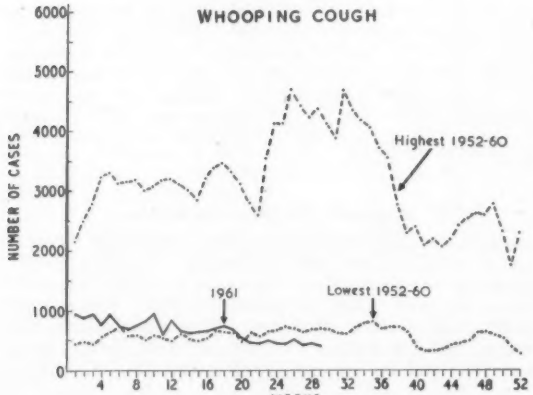
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **July 22** (No. 29) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Engl. & Wales	Lond.	Scot.	N. Ire.	Eire	Engl. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	3	1	2	0		8	0	1	0	
Dysentery	345	24	143	21	6	592	76	218	15	3
Encephalitis, acute	1	0		0		7	0			
Enteric fever:										
Typhoid ..	1	0	1	0		5	1	1	0	
Paratyphoid ..	3	0	2(B)	0		11	3	5(B)	0	2(B)
Food-poisoning ..	191	25	12	0		255	22	27	1	
Infective enteritis or diarrhoea under 2 years				12	28				6	26
Measles*	10,388	185	71	309	187	2,688	163	46	5	22
Meningococcal infection	13	1	7	1		21	2	14	0	1
Ophthalmia neonatorum	15	2	2	0		15	1	5	0	
Pneumonia† ..	118	5	105	2		152	10	95	0	
Poliomyelitis, acute:										
Paralytic ..	11	0	0	} 2		{ 6	1	0	} 0	7
Non-paralytic ..	8	1	0			{ 10	0	1		
Puerperal fever§ ..	165	33	21	1		188	28	13	0	
Scarlet fever ..	308	18	20	12	14	450	27	39	12	16
Tuberculosis:										
Respiratory ..	372	48	40	11		435	33	44	16	
Non-respiratory	73	6	8	4		76	9	8	4	
Whooping-cough ..	397	17	43	10	21	1,601	124	115	4	21

DEATHS	1961					1960				
	Engl. & Wales	Lond.	Scot.	N. Ire.	Eire	Engl. & Wales	Lond.	Scot.	N. Ire	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		2	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	2	1	0	0	4	0	0	0	0
Influenza	4	1	0	0	0	6	1	0	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	338	22	24	13	4	320	14	10	9	4
Poliomyelitis, acute	0	0		0	0	0	0		0	0
Scarlet fever ..	0	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	} 59	{ 7	} 9	{ 0	0	} 50	{ 7	6	1	3
Non-respiratory		{ 1		{ 0	0		{ 1	0	0	0
Whooping-cough ..	0	0	0	0	0	0	0	0	0	0
Deaths 0–1 year ..	252	38	28	7	9	268	28	30	1	6
Deaths (excluding stillbirths) ..	8,293	669	544	127	126	8,331	664	535	95	106
LIVE BIRTHS ..	16,063	1327	1050	303	300	14,860	1309	988	279	430
STILLBIRTHS ..	292	18	29			281	24	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Chair of Psychiatry, University of Birmingham

Professor W. H. TRETHOWAN, professor of psychiatry in the University of Sydney, has been appointed to the Birmingham University chair of psychiatry from a date to be arranged.

Professor Trethowan is 44, and was educated at Oundle; Clare College, Cambridge; and Guy's Hospital Medical School. He gained his M.R.C.P.(Lond.) in 1948, his D.P.M.(Lond.) in 1950. He was elected F.R.A.C.P. in 1961. He served in the R.A.M.C. from 1944 to 1947, and after the war held various appointments at Guy's, the Maudsley Hospital, and the National Hospital, Queen Square. In 1951 he went to the U.S.A. as Fulbright Scholar and assistant psychiatric resident at Massachusetts General Hospital, Boston, and Honorary Teaching Fellow at Harvard University Medical School. He returned to the United Kingdom to become successively lecturer and senior lecturer in psychiatry at the University of Manchester before taking up his present post in 1956. He holds many honorary posts in Australia, and is President of the New South Wales Association of Mental Health.

Chair of Medicine, Cork University College, National University of Ireland

Dr. D. J. O'SULLIVAN, senior registrar in general medicine, United Birmingham Hospitals, and research fellow in medicine, University of Birmingham, has been appointed to the chair of medicine at Cork University College of the National University of Ireland.

Dr. O'Sullivan, who is 35, qualified M.B., B.Ch., B.A.O. (first-class honours) N.U.I., in 1948, gained his M.R.C.P.(Lond.) in 1954, and proceeded M.D.(Honours), Birmingham University, in 1961. His experience at various hospitals in the United Kingdom in general surgery, obstetrics and gynaecology, haematology, and general medicine was followed by a senior registrarship at Birmingham in 1958, and a research appointment in 1960. His publications have been mainly concerned with diabetes.

Emergency Bed Service

As was to be expected after the abnormally quiet year of 1960, 1961 brought a greater volume of work for the Emergency Bed Service. There were 63,461 requests for beds compared with 55,847 in the previous year. The falling trend in fever cases was reversed for the first time in many years, and in the first three months of 1961 there were 2,557 applications for the admission of infectious cases, compared with 1,875 in the corresponding period of 1959 when measles was last prevalent. Considerable difficulty was experienced in finding beds for such patients, and 116 could be admitted only by the medical referee system. The service's *Report for the Year Ended 31st March, 1961*, comments that the run-down of fever beds may have proceeded too far. It is distressed to note that the overall proportion of patients admitted to hospital under the medical referee system was higher (15.2%) than in any previous year except 1956 (15.4%). The maternity problem again causes disquiet, the number of cases dealt with having risen from 2,693 the year before to 3,263.

Medical Association for Prevention of War

The conference on "The Pathogenesis of War," held last month in Cambridge by the Medical Association for the Prevention of War, included sessions on "The Biology of Fighting," "Lessons of History," "Conflicting Ideologies," "Problems of International Co-operation," and "Psychiatric Aspects." Professor L. S. PENROSE, F.R.S., made the point that as preparations for war are largely secret, taking place behind closed frontiers, isolation favours international tension. Co-operation and communication, whether in trade, science, or medicine, tended to reduce the risk of war. Professor A. HADDOW, F.R.S., in the concluding address, stressed that the aims of the M.A.P.W. were not political, religious, or social, but a function of medicine as a whole.

Carlsberg-Wellcome Travelling Research Fellowships

The following workers have been awarded the Carlsberg-Wellcome Fellowships jointly created by the Carlsberg Foundation (Copenhagen) and the Wellcome Trust (London) in 1957:

Dr. EMIL POULSEN (senior lecturer, Royal Veterinary and Agricultural College, Copenhagen) will work at the Medical Research Council's Toxicology Research Unit, Carshalton, on the neurotoxic influence of alicyclic phosphates and similar compounds. Dr. A. F. HAYWARD (anatomy department, Glasgow University) will work at the Carlsberg Laboratory, Copenhagen, under the direction of Dr. H. HOLTER, studying the electron microscopic appearances in pinocytosis. Dr. S. L. ROWLES (member of external scientific staff of Medical Research Council, School of Dental Surgery, Birmingham) will work with Dr. TOVBORG JENSEN, Royal Veterinary and Agricultural College, Copenhagen, on the chemistry of the calcium phosphates, with special reference to those occurring in oral tissues.

World Psychiatric Association

The forty international delegates to the World Psychiatric Congress held in Montreal in June unanimously decided that the Society for the Organization of World Congresses of Psychiatry should be enlarged in scope and re-formed as the World Psychiatric Association. This has now been done, and the first special general assembly of the W.P.A. will be held in 1962 in Geneva, where its headquarters is to be. The following officers have been elected: *President*, Professor EWEN CAMERON (Canada); *vice-president*, Dr. F. G. BRACELAND (U.S.A.); *general secretary*, Dr. H. EY (France); *assistant secretaries*, Dr. WILLIAM SARGANT (Great Britain), Professor J. J. LOPEZ IBOR (Spain); *treasurer*, Professor P. SIVADON (France). An international committee of members from the participating countries has also been formed.

Television for Teaching

A permanent closed-circuit television system, with the camera built into a surgical lamp over the operating table, has been installed at the Queen Elizabeth Hospital, Birmingham. It will enable 40 students at a time to watch operations from an adjoining room. A two-way microphone system allows the surgeon to explain the operation as it proceeds and to give an immediate answer to questions asked by the students.

New Products Under Old Names

The Advertising Association has advised member companies that when both the formula and the purpose of a medicinal product are changed the brand name should also be changed. The new advertising could be misleading because people accustomed to taking the product in its original form may go on buying it without knowing that the formula has been changed. It could also be dangerous because doctors may not be aware of the new formula, and, if they are, they may not know which version the patient has been prescribing for himself and taking.

Memorandum by R.M.P.A.'s Child Psychiatry Section

The Child Psychiatry Section of the Royal Medico-Psychological Association has prepared a short memorandum on "The Functions of the Medical Director of a Child Psychiatry (Child Guidance) Clinic." It considers the medical director's duties under five main headings: (1) clinical, (2) administrative, (3) liaison, (4) teaching, and (5) regional. The honorary secretary of the Child

Psychiatry Section is Dr. J. H. KAHN, R.M.P.A., 11 Chandos Street, Cavendish Square, London W.1.

"Acta Neuropathologica"

The new journal *Acta Neuropathologica* is the official journal of the Commission for Neuropathology and of the Commission for Comparative Neuropathology of the World Federation of Neurology. It will appear in individually priced numbers as the material reaches the press. The editor is Professor F. SEITELBERGER. Professor W. BLACKWOOD is a member of the editorial board, and contributions may be sent to him at the National Hospital, Queen Square, London W.C.1. Inquiries should be sent to the publishers, Springer Verlag, 3 Heidelberger Platz, Berlin-Wilmersdorf, West Berlin, Germany.

Domville Memorial Gift

The Trustees of the Domville Memorial Gift wish to elect a recipient at the beginning of October. The Gift's present value is about £8 a year for three years. The recipient should be (1) a child of a deceased Naval Medical Officer, (2) in necessitous circumstances, and (3) under the age of 15 years at the date of election. Applications, accompanied by a birth certificate and a brief financial statement, should be sent by September 30 to the Honorary Secretary, Domville Memorial Gift, c/o Supply Officer, Royal Naval Hospital, Haslar, Gosport, Hants.

Grants, Gifts, and Bequests

Among the grants made by the Calouste Gulbenkian Foundation, Lisbon, during the first half of the year were a further and final £3,000 a year for three years—in addition to the £9,000 announced in 1957—to the Samaritans, St. Stephen Walbrook, City of London, an organization which assists those tempted to suicide or despair; and £5,000 to the S.O.S. Society towards the cost of additional accommodation for the aftercare and rehabilitation of psychiatric patients at Hill House, Elstree.

People in the News

Dr. B. C. FLATHER, of Newton, British Columbia, has been appointed an Additional Member of the Civil Division of the Most Excellent Order of the British Empire, for gallantry, and G. J. PRIESSLER, a miner, of the same town, has been awarded the George Medal. The citation reads:

"A rock blast at the Howe Sound Company mine caused a rock fall of 6,000 tons to cave-in in the mining floor and the mucking floor of the 49,018-foot slope. A man was trapped in a small pocket of rock and broken timber below the caved-in mining floor. Rescue operations were commenced immediately. Two hours later, George Priessler found an aperture approximately 16 in. square leading underneath the caved slope, and managed to crawl through the hole a distance of 42 ft. and establish contact at a point 12 ft. below the trapped man, who told Priessler that his arm was almost completely shattered at the elbow and that it was bleeding profusely. Priessler crawled back to the east manway safely and reported his findings. After consultation among the miners, it was decided to widen the tunnel Priessler had found and brace it with timber. A natural hole was located leading up through the fallen rock, and it was believed that the man was at the far end of this hole. Priessler entered the hole and found him. Dr. Barrie Flather was brought into the rescue tunnel. After having been warned of the danger of a second rock fall, particularly in the area where the man was trapped, the doctor gave Priessler morphine tablets to take to the casualty. Priessler returned to the tunnel, obtained a lamp and climbed back into the hole for the third time. Dr. Flather then entered the hole. Using a pair of surgical scissors passed up to him, he cut off the injured arm. The operation was performed under very trying conditions. The doctor could not get in beside the trapped man, and was therefore forced to reach in to him. Despite the foul air and the danger of a second rock fall, Dr. Flather entered the tunnel unhesitatingly. He performed the operation under trying and hazardous conditions. Priessler risked his life several times during rescue operations, and displayed outstanding courage and endurance."

Dr. TSEUNG FAT IM's appointment to O.B.E. (Civil Division) for public services in Hong Kong was announced in the Birthday Honours this year. Dr. Tseung Fat Im is a member of the Hong Kong Medical Advisory Board.

COMING EVENTS

Royal Free Hospital.—Dr. R. S. YALOW (New York), "Assay of Insulin," August 16, 5.15 p.m., Royal Free Hospital, Gray's Inn Road, London W.C.1.

Royal Medical Benevolent Fund.—Annual general meeting, September 5, 5 p.m., Medical Society of London, 11 Chandos Street, London W.1.

International Federation of Surgical Colleges.—1961 meeting, Oslo, September 12 to 14, under joint auspices of the surgical associations of Norway, Sweden, Denmark, and Finland. Theme: "Surgical Research." Details and enrolment forms from Secretary and Treasurer of International Federation of Surgical Colleges, Royal College of Surgeons of England, Lincoln's Inn Fields, London W.C.2, by August 14.

Nutrition Society (Scottish Group).—Symposium, "Nutrition and Poultry," September 30, 1.30 p.m., Large Lecture Hall, College of Agriculture, Edinburgh. Details from Honorary Secretary, Dr. D. G. ARMSTRONG, Hannah Dairy Research Institute, Ayr, Scotland.

American Medical Association.—Conference, "Medical Television," Chicago, October 2–6. Details from Mr. R. P. CREER, Director, Department of Medical Motion Pictures and Television, A.M.A., 535 North Dearborn Street, Chicago 10, Illinois, U.S.A.

4th World Congress of Cardiology.—Sponsored by International Society of Cardiology, Mexico City, October 7–13, 1962. Details from Dr. I. COSTERO, Instituto Nacional di Cardiología, 300 Avenida Cuauhtémoc, Mexico 7, D.F.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

BRITISH JOURNAL OF OPHTHALMOLOGY

Pseudotumour of the Orbit. M. E. Coop.
Pathology of an Aphakic Eye Containing an Anterior Chamber Implant. N. Ashton and J. Boberg-Ans.
Aneurysm of the Orbital Part of the Ophthalmic Artery. A. Mortada.
Blindness During Streptomycin and Chloramphenicol Therapy. G. F. Walker.
Treatment of Experimental Trachoma in a Human Volunteer. Ida Mann, C. H. Greer, and D. Perrett.
Lacrimal Abscess in the Newborn. O. O. Ffooks.
Marcus Gunn Phenomenon Associated with Synkinetic Oculo-Palpebral Movements. R. S. Garkal.
Waardenburg's Syndrome. D. K. Ray.
Reviews.
Notes.

Volume 48, No. 8. (Monthly; £6 annually, with *Ophthalmic Literature* and index £9.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, August 15

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Guest lecture by Dr. Barry J. Anson (Chicago): Features of Otological Anatomy Contributory to Problems in Endaural Surgery.

Friday, August 18

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. Howard Nicholson: clinical demonstration.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Bell.—On July 3, 1961, at St. James's Court, Buckingham Gate, London S.W., Kenelm Digby Bell, M.R.C.S., L.R.C.P., Surgeon Captain, R.N., retired.
Brownlees.—On July 23, 1961, Thomas John Kilpatrick Brownlees, M.R.C.S., L.R.C.P., D.P.M., of Exminster, Exeter, Devon, aged 53.
Bullen.—On July 24, 1961, in a nursing-home, Harrogate, Yorks, Charles Henry Bullen, M.D., of Stillington, Yorks, aged 84.
Ironside.—On June 30, 1961, at 54 Skinners Lane, Ashtead, Surrey, Arthur Edmund Ironside, *M.C.* (Bar), M.R.C.S., L.R.C.P., L.D.S., D.P.H., aged 78.
Raitt.—On July 3, 1961, at Foresterhill, Aberdeen, William John Raitt, M.B., Ch.B.
Scarr.—On July 2, 1961, at his home, 131 Manchester Road, Rochdale, Lancs, Ellis Herbert Sydney Scarr, M.R.C.S., L.R.C.P., J.P.
Skeet.—On July 4, 1961, at his home, Jack Garland Skeet, M.R.C.S., L.R.C.P.
Tucker.—On July 5, 1961, at Lynnwood Lodge, Stotfield, Lossiemouth, Morayshire, Hugh Macintyre Tucker, M.B., Ch.B.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

"Gastric Flu"

Q.—*Is there a condition known as gastric influenza which is definitely a form of influenza and not a misnomer for gastro-enteritis?*

A.—"Gastric flu" is not a form of virus influenza. The term is not a good one. It has been coined to describe a disorder consisting of gastro-intestinal disturbance with influenza-like symptoms of fever, headache, and muscle aches and pains. It is a well-recognized condition occurring often in outbreaks, particularly in the winter and spring, but has no aetiological relationship to influenza nor to gastro-enteritis due to Salmonella, Shigella, or pathogenic strains of *Esch. coli*. Influenza is a specific virus infection of the respiratory tract caused by a group of viruses of which there are three main antigenic types A, B, and C. There is no laboratory evidence that any of these viruses, and this includes the numerous immunological subtypes of influenza virus, are responsible for gastric flu. Attempts to isolate other viruses have also been unsuccessful except for one report by Duncan and Hutchison[1] a few weeks ago that adenovirus type 3 had been isolated from several patients in an outbreak of gastric flu, some of which also had symptoms of pharyngoconjunctival fever.[2] Further investigations should show whether or not adenoviruses are aetiological agents in this condition.

REFERENCES

[1] Duncan, I. B. R., and Hutchison, J. G. P., *Lancet*, 1961, **1**, 530.
[2] Bell, J. A., Rowe, W. P., Engler, J. I., Parrott, R. H., and Huebner, R. J., *J. Amer. med. Ass.*, 1955, **157**, 1083.

Sensitivity of N. catarrhalis and Friedländer's Bacillus

Q.—*To which antibiotics are Micrococcus catarrhalis and Friedländer's bacillus sensitive? Which is preferred?*

A.—True *Neisseria catarrhalis* (not always distinguished from *N. crassa* and *N. flava*) is usually at least moderately sensitive to penicillin. Both this organism and *Klebsiella pneumoniae* (Friedländer's bacillus) should be sensitive to streptomycin and tetracyclines. The choice between them rather depends on the condition to be treated, but in an infection of the air passages a tetracycline would perhaps be the most suitable choice. A true "Friedländer" lobar pneumonia might require more vigorous treatment, such as a combination of these two antibiotics.

Stilboestrol and Uterine Scars

Q.—*Is there any conclusive evidence that stilboestrol influences the vascularity and muscular growth of the uterus and thus helps to produce a healthy uterine scar after myomectomy or caesarean section? If so, is it advisable to give stilboestrol post-operatively in these cases?*

A.—Oestrogens do increase the vascularity of the uterus and cause myometrial hyperplasia. This is seen in metropathia haemorrhagica, in which the excessive production of oestrogens is relatively small, and in pregnancy, when the increase is relatively great. But there is no conclusive evidence that post-operative oestrogen administration leads to a sounder scar in the incised uterus, gravid or non-gravid. From a histological study of caesarean-section scars,[1] Hess concluded that healing was mainly by fibrous tissue, especially in the lower segment. In upper-segment scars there were more muscle fibres to be seen. Yet rupture is more likely to occur in late pregnancy and labour in the more vascular, though admittedly more active, upper-segment scar than in the lower. On the other hand, myomectomy scars, though nearly always located in the part of the uterus which goes to form the upper segment, very rarely rupture in labour. Other factors influencing the healing of uterine scars include the technique of suturing, the presence or absence of infection, and the general condition of the patient.

REFERENCE

[1] Hess, O. W., *Surg. Gynec. Obstet.*, 1953, **96**, 584.

Loss of Hair in Women

Q.—*A healthy married woman aged 37 with two children has sustained a gradual thinning of the hair over the past 5 years. This is now very pronounced, especially on the crown. Is any particular treatment (e.g., endocrine) indicated?*

A.—In both men and women the pattern of loss of hair and its age of onset are, to a large extent, genetically determined. A family history of premature thinning of the hair implies a poor prognosis. Androgens can induce a male pattern of loss of hair in women, but if the menstrual cycle is normal, and there are no other signs of virilization, an endocrine cause is unlikely. The type of alopecia described in this patient is becoming increasingly common.[1] The loss of hair is diffuse but is often most obvious on the vertex. Stress and fatigue, acting through a pituitary/suprarenal mechanism, have been suggested as its cause, but scientific proof is not available. Certainly some such patients show a gradual improvement after a holiday, or when a period of stress comes to an end. Treatment is extremely disappointing. Endocrine therapy has no rational basis, and topical applications, including ultra-violet light, are ineffective. Fortunately many patients recover spontaneously.

REFERENCE

[1] Sulzberger, M. B., Witten, V. H., and Kopf, A. W., *A.M.A. Arch. Derm.*, 1960, **81**, 556.

Syringes for Intrathecal Injections

Q.—*I have heard that minute traces of detergents, such as "teepol," used in washing syringes might have a harmful effect if injected into the central nervous system. Can you confirm this, and, if so, would ordinary soap be a safe substitute?*

A.—Teepol can cause a dermatitis and a good soap will not. It may perhaps be concluded from this that tissues much more susceptible to damage will react in a relatively similar way. On the other hand, the idea of using for an intrathecal injection a syringe in which even traces of a cleaning material remain is quite horrifying. Thorough and repeated rinsing in distilled water is necessary after using such an agent in any case, but surely a syringe used for this of all purposes should be reserved for types of use which obviate the necessity for any such cleaning?

Drugs Acting on Striated Muscle

Q.—*What drugs have a paralytic action on the contractile element of muscle fibres as opposed to those which act on neuromuscular junctions?*

A.—For a proper understanding of the action of drugs on striated muscle it is necessary to consider the physiological processes which are known to occur when muscle contraction takes place. Briefly, when a motor impulse arrives at the nerve ending acetylcholine is released. This substance then enters by diffusion into the postjunctional end-plate and combines with specific receptors at the muscle end-plate. The latter then becomes permeable to all ions and depolarization of the end-plate occurs, giving rise to the end-plate potential. Within a few milliseconds the acetylcholine is removed mainly by hydrolysis by the enzyme cholinesterase. When the end-plate potential reaches a critical amplitude it activates the adjacent muscle membrane and causes a propagated potential change, the action potential of the muscle. This triggers the contractile

elements of the muscle, and muscular contraction occurs. The precise nature of the mechanisms responsible for this step are still unknown. Drugs which paralyse muscle may do so in one of three ways: (1) by interfering with the release of the transmitter substance (acetylcholine); (2) by interfering with the processes concerned in the development of the end-plate potential and its propagation; and (3) by affecting the excitability of the muscle membrane and the contractile elements of the muscle fibre. The majority of drugs which are used as muscle relaxants belong to the second group. They paralyse the muscle either by competition block—i.e., they "compete" with acetylcholine for the receptors on the motor end-plates (e.g., tubocurarine) or by causing prolonged depolarization (e.g., the methonium compounds) or by destroying cholinesterase (e.g., prostigmin). Substances which prevent the release of acetylcholine are magnesium and calcium ions in excess and botulinum toxin. Relatively few drugs are known to affect the activity of the muscle membrane and the muscle fibres themselves, and those that do so—e.g., the veratrum alkaloids—alter the excitability but do not cause paralysis. Hypnotic drugs such as the barbiturates have been shown to increase the threshold of the muscle membrane and to reduce, and finally to abolish, the action potential of muscle. Certain other drugs such as quinine and caffeine may also have some direct action on the muscle fibre. An excellent review of this subject has recently been published.[1]

REFERENCE

[1] Thesleff, S., in *The Structure and Function of Muscle*, ed. G. H. Bourne, 1960, Vol. III, p. 1. Academic Press, New York and London.

Carcinoma of Prostate and Sexual Intercourse

Q.—*Is sexual intercourse contraindicated in a man whose prostate on removal was found to have malignant changes? His wife has sexual desires which he is anxious to attempt to satisfy if it will not aggravate his potentially malignant condition. He is on stilboestrol.*

A.—I know of no evidence that suggests that malignant disease can be transmitted by a man suffering from carcinoma of the prostate to his wife during sexual intercourse, nor do I know of any evidence that sexual intercourse would aggravate the malignant condition. On the other hand, stilboestrol reduces sexual desire and sometimes abolishes it altogether, so that on those grounds intercourse may be impracticable.

Aluminium Cooking Utensils

Q.—*Is there any evidence that aluminium cooking utensils can cause chronic aluminium poisoning with gastro-intestinal symptoms like gastritis, ulcer, colitis, etc., unrecognizable from similar symptoms of other origin? Is there any laboratory method by which chronic aluminium poisoning can be diagnosed?*

A.—The toxicology of aluminium has recently been reviewed by Browning,[1] who confirms the verdict of the American Medical Association Council on Foods and Nutrition that "the use of aluminium cooking utensils is in no way injurious to health."[2] There is no reliable evidence that aluminium by mouth in man causes the conditions described by the questioner, and there is no standard laboratory test for chronic aluminium poisoning.

REFERENCES

[1] Browning E., *Toxicity of Industrial Metals*, 1961. Butterworth, London.
[2] *J. Amer. med. Ass.*, 1951, **146**, 477.

Oxytocin Infusion in A.P.H.

Q.—*Is an oxytocin infusion permissible in a patient who has had a severe accidental haemorrhage with intrauterine foetal death and who does not go into labour after resuscitation and artificial rupture of the membranes?*

A.—An oxytocin infusion is permissible. As weak an intravenous drip as 1 in 8,000 (1¼ units oxytocin in 1 litre 5% glucose) will probably suffice, but double this strength may be used if necessary. It should be kept available to counteract any later tendency to post-partum haemorrhage, either by being continued as slowly as practicable throughout labour or, better, by being connected to a Y-tube the other arm of which runs to a bottle of other infusion (e.g., blood, plasma) so that the oxytocin administration can be halted when indicated and resumed easily when required. During the whole of this time a watch should be kept against dangerous hypofibrinogenaemia.[1]

REFERENCE

[1] Holland, E., and Bourne, A. (Editors), *British Obstetric and Gynaecological Practice*, 2nd ed., 1959. Heinemann, London.

Garlic in Pulmonary Conditions

Q.—*Is garlic of any value in pulmonary conditions such as bronchitis and bronchiectasis?*

A.—A short answer to the question is "No." Presumably the suggestion that it is of some benefit arises from the past idea that any substance which imparts a smell to the breath must in some way be beneficial to respiratory diseases: but we have come past this sort of medicine now. If garlic were used to disguise the fetor of bronchiectasis this would be bad medicine. It can be controlled by chemotherapy nowadays.

NOTES AND COMMENTS

First Aid for Chemical Burns of the Eye.—Dr. L. GWYNNE MORGAN (Richard Thomas and Baldwins Ltd., Ebbw Vale, Mon.) writes: In his answer to the question on first aid for chemical burns of the eye ("Any Questions?" July 1, p. 66) your expert stated that there is no universal antidote for acid and alkaline burns. In this steelworks eight years' experience has shown that when the water lavage is rapidly followed by washing with phosphate buffer solution there is a considerable reduction in the amount of local reaction and tissue damage. The recovery time is shortened and there are very few cases with any permanent disability. The solution used is:

Potassium dihydrogen phosphate ..	70 g.
Disodium hydrogen phosphate ..	180 g.
Water	850 cc.

Hazards of Electric Blankets.—Mr. P. MCEWAN (Bradford) writes: In order to make an electric blanket safe for use by an incontinent patient ("Any Questions?" May 27, p. 1556) it is sufficient to place the blanket above the patient instead of beneath him. It will be equally effective in warming the bed and the patient. If it is too heavy it can be put on top of the blankets and gently tilted on to the floor by the patient before he goes to sleep.

Treatment of Stings.—Dr. J. A. HADFIELD (London) writes: I am a bee-keeper, and at spring-cleaning and also at collection of honey I often get ten, or more bee stings, to which I am not immune (see "Any Questions?" July 8, p. 125). One or sometimes two antihistamine tablets are enough to allay all after-effects. A child under one year of age was stung last year and was given one-quarter of a tablet: other children of 3–6 have been given half a tablet, and no more was heard of the sting.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volume 3 (26s. 9d.).
Any Questions?, Volume 3 (8s. 3d.).

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON W.C.1. TELEPHONE: EUSTON 4499. TELEGRAMS: *Aitiology, Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

Authors desiring REPRINTS should communicate with the Publishing Manager, B.M.A. House, Tavistock Square, W.C.1, on receipt of proofs. Authors overseas should indicate on MSS, if reprints are required, as proofs are not sent abroad.

ADVERTISEMENTS should be addressed to the Advertisement Director, B.M.A. House, Tavistock Square, London W.C.1 (hours 9 a.m. to 5 p.m.). TELEPHONE: EUSTON 4499. TELEGRAMS: *Britmedads, Westcent, London.*

MEMBERS' SUBSCRIPTIONS should be sent to the SECRETARY of the Association. TELEPHONE: EUSTON 4499. TELEGRAMS: *Medisecra, Westcent, London.*

B.M.A. SCOTTISH OFFICE: 7 Drumsheugh Gardens, Edinburgh.